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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 28 1961

DRUGS IN THE TREATMENT OF DEPRESSION*

BY

WILLIAM SARGANT, F.R.C.P.

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When I began working in a large London general teaching hospital, after spending my earlier years in psychiatry at specialized psychiatric hospitals, I very soon started to realize that in the large numbers of treatable cases of depression being seen by general practitioners and physicians everywhere the diagnosis may be overlooked for long periods of time. These are not the severe cases of melancholia so easily recognizable by everybody and sent on early for specialized psychiatric treatment. They are the far more numerous patients with milder and more atypical depressive illnesses, sometimes diagnosed as anxiety states, many of whom get sent to general hospitals for all sorts of investigations because they complain of pains or other disturbances in almost every bodily organ. They, and often their doctors, think that their feelings of depression are caused by these bodily disturbances instead of being, of course, the other way round. What so often happens, after all tests and examinations are found to be normal, is that they are strongly reassured that there is nothing at all the matter with them, and nothing else is then done. And so they go away feeling just as ill and depressed, and even more hopeless than ever.

The fatal toll of suicides is mounting ever higher and higher in this country, so that over 5,000 people are now killing themselves annually. And large numbers of these are just such depressed patients who have already been seen by doctors and who have obtained so very little help from them that suicide seems the only way out of their problems and suffering.

This tragic state of affairs, however, coincides with the fact that depressive illnesses are now the most easily treatable and also have the highest potential for recovery of all types of mental illness. Patients can nearly always be helped out of an attack of depression, most of them fairly speedily, if only the correct diagnosis is made and the appropriate treatments are given.

Antidepressant Drugs

Most of you already know about older advances such as the use of electric shock, modified leucotomy, sleep, and modified insulin treatments in depressive states, but much less is known as yet about the proper use of what may well become another major advance in the treatment of the depressions—namely, the recent discovery of a whole new range of antidepressant drugs. And it does seem that these are now bringing to a large number of depressions of a certain type the possibilities of easy and effective treatment by general practitioners and general physicians alike.

Now, drug manufacturers are aware—often much more so than many doctors—of the enormous number of patients with depression needing help, and with the advent of these new antidepressant drugs their advertising pressure upon us all has become very serious indeed. Just as happened when the new tranquillizers were introduced, foolish and absurd claims were made for their value in quite the wrong types of patient, so we are again seeing at the present time an intensive advertising of the new antidepressant drugs for cases of depression in which they may be quite unsuitable, and if used can only increase the grave risks of suicide always present in severe depressive illnesses. And because the chemical treatment of depression is now becoming such "big business," each drug firm is trying to produce its own slightly different antidepressant drug, and sometimes claiming advantages over its equally and sometimes more efficient rivals, and altogether adding chaos to the present confusion about the real value of all these preparations.

Fortunately, at St. Thomas's we have for nearly three years been able to test, often in advance of their general use, many of these drugs, and they are being produced in still greater numbers and varieties. In fact, it is becoming difficult to cope properly with all of them, and some are being rushed on to the market, I am afraid, with very little testing indeed in this country (Dally and Rohde, 1961).

The general overall position about their uses and abuses is, I think, now becoming much clearer. Most of the advertising which suggests that these drugs are valuable in the treatment of depressions in general is not true; for most of them do not really help many of these patients, who are so obviously depressed that even the relatively untrained practitioner and general physician can see this immediately. In other words, the classical melancholic depressions—those depressions needing, and often being so quickly and certainly helped by, electric shock treatment—are far from being always helped by the new antidepressant drugs.

However, some evidence is accumulating which suggests that if electrical treatments are combined with the use of one or other of the appropriate antidepressant drugs, then sometimes the number of electrical treatments otherwise needed may be reduced. Also, some patients with severe depression respond to electric shock and then tend to relapse again quickly afterwards; and it also seems that if the antidepressant drugs are used after electric shock treatment has been stopped the

*A paper given at the Annual Clinical Meeting of the British Medical Association, Middlesbrough, 1960.

relapse rate may not be as great. Furthermore, there are occasional patients with deep endogenous depressions who, after the failure of electric shock earlier on in an attack, do seem to be greatly helped towards the end of their attacks by the use of these new chemical agents. But it has not yet been possible, for instance, to show that the actual number of patients needing out-patient and in-patient E.C.T. at St. Thomas's has greatly lessened with the advent of the new antidepressant drugs, though we use them very intensively. Claims being made that these drugs are as effective as E.C.T. and can replace it are both misleading and dangerous.

Advantages of Antidepressants

Where, then, do the great advantages of some of the antidepressant drugs lie? Apart from those already mentioned, it is, paradoxically, in a group of depressions which have received practically no descriptive publicity or special advertising from the drug manufacturers. But they constitute a very much larger group of patients who are seen every day by general practitioners and psychiatrists alike, and who, up to recently, have often constituted a very difficult diagnostic and therapeutic problem for us all. They are what have been termed by West and Dally (1959) at St. Thomas's the "atypical" or "hysterical" types of depression, or they could alternatively be labelled as patients suffering from neurotic or reactive depressive illnesses or even sometimes from anxiety hysteria. Most of you will quickly recognize the sort of patient I mean when I describe them.

They are patients of *known good previous personality* who may have been through some special or prolonged stress or experienced a great shock. They have then suddenly or gradually become much more emotionally unstable. They have insight, and bitterly deplore the fact that whereas they used to be in control of their emotions, now their emotional moods have taken control over them. One day they are depressed or anxious, and the next day they may feel better again, often for no apparent reason at all. Unlike the true endogenous depressives, their sleep may not be much curtailed by early morning waking, but after a long night's sleep they say that they wake up just as fatigued and as tired as ever. Others complain of a poor quality of sleep, of disturbing dreams, and of general restlessness. General fatigue is also one of the symptoms of which they so bitterly complain, and they contrast their present tiredness and lethargy with their normal state, when they are usually most energetic and active people. It is this feeling of extreme fatigue which often stops them from coping with the simple daily duties that used to come so easily, and they may become fearful of the simplest tasks. Irritability also becomes exaggerated, and, unlike most true depressives, they blame others as well as themselves. Women in this group also complain frequently of severe premenstrual tension or depression. There may even be a marked hysterical exaggeration of symptoms when ill, though they are not hysterical people when well. And often, too, there has been a very considerable associated loss of weight.

Despite the fact that the patient is one who has usually faced up to the normal worries and problems of daily living, he has now ceased to be able to do so, and one often feels that he needs some sort of psychotherapy because he seems incapable of dealing with the environmental troubles that can beset us all at times. And in the past this is what so often had to be suggested in the way of treatment, since little else helped them; left alone, many will gradually emerge spontaneously from their reactive depressive state with time, but their incapacity may last for months or even years.

Monoaminase Inhibitors

Now, it is just these atypical or hysterically depressed patients with good previous personalities who, if treated with some of the new antidepressant drugs, may show such remarkable improvements even in the matter of a very few days. Iproniazid ("marsilid") is one of the most effective of this particular group of what are called monoamine-oxidase inhibitors, but the danger of a severe toxic jaundice in one in 250 patients makes it undesirable, except with special precautions and in those rare cases that should respond but are found quite resistant to all the other drugs now available in this group.

We have found phenelzine ("nardil"), 15 mg. t.d.s. to q.d.s., and isocarboxazid ("marplan"), 10 mg. t.d.s. to q.d.s., to be the most practical, efficacious, and safe amino-oxidase inhibitors for general use, though neither is as effective as iproniazid. We have not found nialamide ("niamid") to be as good as phenelzine or isocarboxazid in the cases described above; and, although pheniprazine hydrochloride ("cavodil") can be effective, yet its complications seem greater and can be more disturbing to the patient than the other two already mentioned. The most common complication of phenelzine, isocarboxazid, and others in this group is postural hypotension and the occurrence of giddiness or feelings of faintness on getting up or on moving quickly. This may mean having to lower the dose; and sensitivity differs from person to person. Finding the correct dose for each patient is very important because of the side-effects when too much is given. Fortunately, toxic jaundice has not yet been reported with the use of phenelzine or isocarboxazid as it has with iproniazid and pheniprazine.

If one is going to get a good result in these atypical depressions, it will generally start in the first week or ten days. Feelings of fatigue rapidly lessen, and patients again begin to face normal problems easily. Generally, improvement will start as early as the third or fourth day with this betterment in the feeling of fatigue; sleep may also improve (though it worsens in some patients initially), and feelings of tension also start to lessen. Sometimes there is a rapid switch-over to feelings of great well-being and, rarely, to actual hypomania.

In some cases the drug can be stopped as soon as the patient feels better again, but in most a rather longer period of maintenance treatment is needed, with a gradual tailing off after a month or so. Some more chronically depressed patients feel so much better on the drug, and so much worse when it is stopped again, that its use can be continued for months on end with obvious benefit. Relapse may start only two to three days after the drug has been stopped or lowered too much, and not immediately, and unless this is realized the relation between a relapse and the stopping of the drug may be missed. So far there seem to have been no undesirable complications with the prolonged use of these drugs, and addiction to increasing the dose is not acquired, since raising the dose produces unpleasant side-effects.

This same group of monoamine-oxidase inhibitors can also be used to try to prevent the recurrence of the

more neurotic types of depressive symptoms in patients who suffer from such periodic depressions. These drugs may be given in small doses all through the normal phase, and the dose increased as soon as the depressive phase comes on and until it lifts again. Before the introduction of these drugs there was no real means of helping such unfortunate patients, and even now we may not be able to stop the attacks in deeper recurrent depressions, only the depth of the attack being perhaps lightened or shortened.

Imipramine

Another of the new and widely publicized antidepressant drugs, imipramine ("tofranil"), is not an amino-oxidase inhibitor and is more closely allied to the chlorpromazine ("largactil") group of drugs. On the whole, it is far more effective in the more endogenous types of depression, but is of less value in the neurotic types of depression already discussed. It also generally takes longer to work. The dose needed may vary from 25 to 75 mg. t.d.s., and it can undoubtedly bring some of the milder cases of endogenous depression out of their attacks without the need for electric shock treatment; but one may have to wait for up to a month for this to happen, and in most cases of deeper endogenous depression E.C.T. is still desirable. To put deeply depressed patients on imipramine alone, and to leave them too long on it while awaiting possible improvement, may actually result in a marked worsening of symptoms and in what should have been a quite unnecessary suicidal attempt.

Imipramine can, however, be useful in helping to maintain recovery after the use of E.C.T. and in preventing future attacks. And, as already mentioned, there is now some evidence that the giving of imipramine during the course of E.C.T. may diminish the number of treatments otherwise needed; and this, too, applies to some of the monoamine-oxidase inhibitors, such as phenelzine and isocarboxazid. In cases in which there is doubt regarding which group of drugs is the most efficacious in a particular patient, one can sometimes combine, say, phenelzine and imipramine, and even give both of them together with E.C.T. Here, however, there is naturally a greater risk of postural hypotensive effects and other complications. But some patients do seem to tolerate quite large combined doses, such as imipramine mg. 25–50 t.d.s. and phenelzine mg. 15 t.d.s., very well indeed.

Outlook for the Future

What do all these advances mean for the future? Well, when I first entered psychiatry in 1934 there were no effective treatments of depression, and, just as now, psychotherapy was showing itself to be a most uncertain and very limited form of treatment in this large group of illnesses. But in the past twenty-five years one has seen what has amounted to a total revolution in treatment. Unfortunately, the training of medical students in the recognition of even such common psychiatric illnesses as simple depressions has been so deplorable because of the lack of time so often allowed in the medical curriculum that it will be impossible for some time to come for us to take full advantage of all the significant advances in treatment that have been made in recent years. However, if the various types of depressed patients can only be recognized early and distinguished one from the other by general doctors, numbers of neurotic depressions in people with good previous personalities, and some endogenous ones as well, can now be quickly and effectively treated by the use of some of the new antidepressant drugs in the way I have described.

Other advances such as E.C.T., the provision of better and more varied types of long- and short-acting barbiturates, all the amphetamine drugs, the new tranquillizers, the use of modified insulin, and, when everything else has failed, a consideration of the most successful new and more modified forms of leucotomy—all such advances make the actual position to-day one in which there are very few cases of depression indeed, either acute or chronic, and occurring in good previous personalities which cannot be helped back to renewed efficiency and happiness in living. The skill, however, must still lie in the proper selection of patients for all the varied types of physical treatment now available to us, and a much longer paper would be needed to exhaust this whole fascinating and important topic.

Conclusion

I do believe, however, that all these recent physical advances in the treatment of depression also spotlight what must almost inevitably happen in most other major psychiatric illnesses in the years to come. For we are bound to discover more and more empirical physical methods of treatment to help them, and we shall also continue to learn more about their fundamental physiological nature and causes. I still remain quite unrepentant in my beliefs that a lot of our present-day specialized psychiatric and psychotherapeutic treatments will become more and more unnecessary in the future. And the next twenty-five years will see very many more of our patients able to go back and be treated quite simply and easily by the general practitioner and general physician using ordinary medical methods.

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"ACUTE WHEEZY CHESTS"

CLINICAL PATTERNS AND NATURAL HISTORY

BY

JOHN FRY, M.D., F.R.C.S.

General Practitioner, Beckenham, Kent

The management of the patient with a "wheezy chest" is a common problem in British medical practice to-day, as it has been for many centuries past. According to my own estimate and that of others (Goodall, 1958; Fletcher *et al.*, 1959), the family doctor in an average-sized practice (2,500) may expect to see in any year between 100 and 150 patients complaining of wheezing in their chests and shortness of breath, and of these some 40 to 50 will be seen for acute and distressing episodes of wheezing and breathlessness. It is these acute episodes that cause most of the troubles for the patient and most of the problems for the doctor, and it is with this group of cases that the present paper is concerned.

A non-specific term such as "acute wheezy chest" has been used on purpose rather than terms such as "asthma" or "bronchitis," because it was intended to study a clinical syndrome and not a specially delineated group such as "asthma."

The needs to study "acute wheezy chests" are obvious to anyone engaged in active medical practice, for there are many questions to which we have had no clear answers. What do these acute episodes signify and what are their implications? What happens to the individual patients? How many go on with attacks and end up as respiratory cripples and invalids? How many "grow out of" their attacks and become symptom-free? The answers to these questions cannot be found in any standard textbooks, and it is only from years of observation that one gains the experience from which to build up clinical opinions and impressions.

This study was undertaken to record the progress of patients who have suffered from "acute wheezy chests" in a general practice and to analyse their course and progress so that some factual evidence may be available to support clinical opinions and impressions.

Aims and Methods

The importance of defining clinical patterns of "acute wheezy chests" and observing the natural history has already been noted, and it is this that has been attempted in a general practice.

In a general practice a follow-up extending over many years is a relatively easy matter, since the patients and their families are seen regularly, and up-to-date information on the patient under review is always available. The mechanics of the project presented few problems.

A period of 10 years (1949–58) was taken, and during this period all patients with "acute wheezy chests" were picked out, information on them recorded on special cards, and then the patients were followed up over the years. Only those patients were included who had been observed for five years or longer, and who were still in the practice at the end of the period (1959).

During this period 21 children (in addition to the 126 observed) and 12 asthmatics (in addition to the 98 observed) moved out of the area of the practice. Of these asthmatics, only two were severely affected. There was no suggestion of any significant number of asthmatics moving out or changing to another doctor for treatment.

An acute wheezy chest was defined for the purposes of this study as an acute episode with sudden onset, or sudden worsening, of wheezing in the chest accompanied by breathlessness. On auscultation high-pitched rhonchi were heard in all the patients' chests.

When patients suffering from acute wheezy chest were seen, all ages and all types being included, they were included in the study. Details were noted of the attacks, their onset and progression, and of family history and past illnesses. Treatment was noted. The patients' progress over the years was carefully observed and the number of recurrences recorded. At the end of the period of observation the patients were graded functionally. The system of grading was one adapted from Harris (1955) and Bruce Pearson (1958).

Grade 1: no attacks for three years.

Grade 2: minor attacks controlled by simple treatment and causing no interference with normal life and routine.

Grade 3: occasional severe attacks with some loss of time from school or work.

Grade 4: frequent severe attacks causing much interference with school attendance or work.

Grade 5: complete invalids unable to carry out work or attend school, or deaths from pulmonary failure.

The Practice

Information on the practice is naturally of importance as a background of the type of community where the patients lived. It is situated in the south-eastern London suburbs with a typical social grouping as shown in Table I (males only). The average size of the practice is shown in Table II.

TABLE I.—*Social Class Distribution of Practice (Males Only)*

Social Class:	I	II	III	IV	V	Not Known	Total
No. ..	99	476	1,522	100	109	26	2,432
%	4	18	63	4	5	6	100

TABLE II.—*Average Population at Risk*

Age:	0–	5–	10–	20–	30–	40–	50–	60–	70+	Total
Males ..	199	221	259	349	383	396	321	167	137	2,432
Females ..	189	188	346	362	438	391	327	224	150	2,615
Total ..	388	409	605	711	821	787	648	391	287	5,047

Table III gives some idea of the annual prevalence of all types of acute wheezy chests. This has taken into account all cases, including those who moved in and out of the practice. Some patients were inevitably included more than once because of recurrent attacks. The annual prevalence rate of 20 per 1,000 means that in this particular practice just over 100 episodes were treated every year. The age distribution shows the particular susceptibility of the young and old.

TABLE III.—*Annual Prevalence Rate per* 1,000 *at Risk* (1949–58)

Age:	0–	5–	10–	20–	30–	40–	50–	60–	70+	Total
Rate per 1,000 ..	32	25	15	5	5	15	20	35	75	20

Clinical Groups

Over the 10 years (1949–58) 327 individual patients suffering from an acute wheezy chest were seen and followed up for at least five years. As time went on it was found that these patients, with their attacks, could be classified into three clinical groups: wheezy children, 126; asthmatics, 98; chronic bronchitics, 121. 18 patients were included in more than one group: 12 wheezy children were eventually diagnosed as asthmatic and were also included in that group, and six asthmatics were also considered to be suffering from chronic bronchitis. The criteria for the three groups were as follows:

Wheezy Children.—This group included all acute wheezy episodes in children in their first decade. No attempt was made initially to diagnose "asthma," but it was found on follow-up that 12 of the 126 (nearly 10%) were eventually labelled "asthmatics." Since in 92% of cases in this group the attacks were preceded by an upper respiratory infection, these attacks were probably examples of an acute bronchitis with wheezing.

Asthma.—Although over a period of time it was quite easy to recognize a case of "asthma," a definition of "asthma" is not easy. In this survey asthma was diagnosed when the patient experienced paroxysmal recurrent acute episodes of wheezing that were not always related to an associated acute or chronic respiratory infection.

Chronic bronchitis was recognized to be present when the patient gave a history of cough and sputum had

been present for at least three consecutive months every year for at least three years.

Delineation of these three clinical groups was very useful in practice. Wheezy children and asthmatics are dealt with below, but it was not possible to do this in the case of chronic bronchitics because of difficulties of definition. A separate study of chronic bronchitics is planned.

Wheezy Children

Over the period of 10 years 126 children (aged 0 to 10) out of an average 797 at risk suffered an acute wheezy chest. This gives an incidence rate of 160 per 1,000, or 16%. This figure is not extraordinarily high, as Goodall's (1958) rate was 22% of 1,726 children in his Yorkshire practice. It seems, therefore, that at least one child in five suffers from acute wheezy episode at some time during the first 10 years of life.

These 126 children were observed in 214 attacks, and in no fewer than 198 (92%) of these attacks there was a preceding acute upper respiratory infection. These attacks were probably examples of a descending acute bronchitis in which wheezing was a prominent feature. The attacks were characterized by sudden onset, with malaise, fever, cough, wheezing, and breathlessness. The attacks varied in severity. Boys (70) were more often affected than girls (56). In just over one-third (39%) there was a history of some other allergic disorder such as eczema, urticaria, or allergic rhinitis.

Age at Onset.—The age at which attacks first began is shown in Table IV, and it is evident that in the majority (87%) their attacks had started by the age of 6 years. There appeared to be peaks in levels of incidence in the first year and in the pre-school period.

TABLE IV.—*Age at Onset of Acute Wheezy Chests in Children (0–10)*

Age:	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–10	Total
No.	26	18	11	20	18	17	8	7	1	—	126
% ..	21	14	9	16	14	13	6	6	1	—	100

Frequency of Attacks and Recurrences.—These 126 children suffered 214 attacks. Table V gives the incidence of these attacks at various ages. The peak was in the pre-school period and during the first year at school, with a marked decline after the eighth year, a decline that continued in the adolescent years. The number of recurrent attacks is shown in Table VI. As many as 80

TABLE V.—*Incidence of Acute Wheezy Chest Attacks in Children 0–10 Years*

Age:	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–10	Total
No. of attacks	26	20	15	29	30	28	16	25	19	6	214
% of those at risk	34	24	20	35	43	35	20	30	24	7	27%

TABLE VI.—*Recurrent Attacks of Acute Wheezy Chest in Children (0–10)*

No. Attacks:	1	2	3	4	5	6+	Total
No. of individuals ..	80	25	10	6	3	2	126
Total attacks ..	80	50	30	24	15	15	214

children (63% of total) experienced only a single attack of wheezing with no recurrence during the period of observation, and only 11 children (8%) suffered more than three attacks.

Course.—At the end of the period of observation, in 1959, a functional assessment and grading was made of these 126 children by the method already noted. The results are shown in Table VII.

TABLE VII.—*Functional Grading of Wheezy Children After 5–10 Years of Observation*

Grade:	1	2	3	4	5	Total
No. of individuals	108	12	5	1	—	126
% of total ..	87	9	3	1	—	100

The outlook for these wheezy children was favourable. At the end of 5 to 10 years of observation 87% had ceased to suffer attacks altogether, 9% had very minor and insignificant attacks, 3% still had acute episodes that involved periods away from school, and only one child was in any way severely incapacitated by frequently severe episodes. These children were all treated at home and attended normal schools. The treatment was kept as simple as possible and was based on antispasmodics such as ephedrine and antibiotics (penicillin by intramuscular injection) where indicated. Asthma was eventually diagnosed in 12 (10%) of these children, but, even so, only 6 (5%) continued having attacks after their tenth birthday.

Comments

The fact that approximately 20% of children in two distinct areas suffered from acute wheezy chests during their first decade underlines the importance of the condition. The reasons why it should be so frequent in young children are probably related to special anatomical, physiological, and pathological factors.

The statement made by Chevalier Jackson that "all that wheezes is not asthma" was borne out in these wheezy children, for only 10% were diagnosed as asthmatic.

Observations on the course of these wheezy attacks showed that the prognosis was excellent. Since the treatment given was simple and non-specific, and aimed at relieving the wheezing whenever it occurred, it must be concluded that the satisfactory outcome must have represented the true natural history of the disorder. Only one single attack occurred in as many as 63% of the children, and only 8% had more than three attacks over the 10 years. By the age of 10, 87% of the children had ceased to suffer any attacks at all, 9% had very minor episodes, and only 4% were inconvenienced by the disorder.

Goodall (1958) found a very similar pattern of prognosis—over 80% of children had ceased to wheeze by the age of 10 and 95% by the age of 15.

It is quite justifiable, therefore, to give parents of wheezy children a good prognosis and reassure them that their children are not likely to become asthmatic.

Asthma

Asthma was diagnosed when recurring acute attacks of wheezing and breathlessness occurred paroxysmally and unassociated with either acute upper respiratory infections or chronic bronchitis. This somewhat vague and rather exclusory definition was found to be useful and practical in general practice, where from long periods of observation the diagnosis could always be confirmed with certainty over the years. Some interchange of cases between the clinical groups has already been noted; 12 wheezy children were finally placed in the asthma group, and six asthmatics were thought to be suffering from chronic bronchitis.

Frequency.—Over the 10 years (1949–58) in an average population of 5,047 there were 98 patients diagnosed as suffering from asthma and followed up for at least five years. This represents an incidence rate of 20 per 1,000. The rate would have been higher if those who had moved in and out of the practice over this time had been included. It is a little difficult to compare these figures with others, because our figures covered a period of 5 to 10 years and because there is really only one other reliable source, and that is the report of Logan and Cushion (1958) on a study of one year's records of over 100 family doctors. Here the incidence rate for asthma *over a period of one year* was 10 per 1,000. In the present study of these 98 patients an average of 51 required medical attention in any year, which gives an almost identical *annual* incidence rate of 11 per 1,000.

Age at Onset

Table VIII shows the ages at which attacks of asthma began in these 98 patients. In 53% they started in the first 10 years of life. The apparent paradox that while 53% of asthmatics began their attacks in their first decade and that only 5% of wheezy cases went on to asthma is explained by the different groups of patients that were being considered. The asthmatics were not only children but adults whose attacks had started in childhood and who had not been included in the groups of wheezy children that were being studied. In other words, the asthmatics came from a much larger population at risk (5,047) than did the wheezy children (797).

TABLE VIII.—*Age at Onset of Asthma*

Age:	0–	10–	20–	30–	40–	50–	60+	Total
Males ..	32	4	4	3	4	1	—	48
Females ..	20	4	10	10	2	3	1	50
Total ..	52	8	14	13	6	4	1	98

This early commencement of asthma has been noted by other authors writing from the hospital and consultant fields. Onset in the first 10 years of life was found in 40% by Bruce Pearson (1958), in 33% by Williams and Williams (1949), in 56% by Williams *et al.* (1958), and in 49% by Kauntze *et al.* (1951). It appears that between one-half and one-third of asthmatics begin their troubles in childhood.

Sex Incidence

Another interesting feature was the sex incidence. There was little difference between the sexes over the whole series (48 males and 50 females), but there were appreciable differences in the various periods at which the attacks began. In the first decade asthma began much more frequently in boys than in girls (3:2). Over the age of 20 twice as many females began to have asthma as did males. Similar trends were observed by Williams and Williams (1949), Bruce Pearson (1958), and Williams *et al.* (1958).

Course

What happens to our asthmatic patients? How many go on to become pulmonary invalids? How many cease to suffer attacks? These are important questions, and an attempt is made here to answer them.

All the patients were observed continually for at least five years, but many for much longer periods. Also, many came into the practice some time after having their first attacks, so altogether a good composite picture was obtained. Since there is no satisfactory specific therapy for asthma these patients were treated for the attacks with antispasmodics and antibiotics when necessary. No attempts were made to desensitize the patients or to give any special psychotherapy or other pseudospecific treatment. The follow-up and assessment represents a picture of the natural history of asthma.

A functional assessment and grading was made, using the system described, at the end of the period, in 1959 (Table IX). It will be seen that the peak severity (which occurred some three to seven years from the onset) was associated with a disability rate of approximately 96% —that is, grade 3 or worse. However, 5 to 10 years later this disability rate fell to a mere 10%, showing that there is a natural trend for asthma to improve with time. Of course, there are individual patients who do not improve, who remain disabled or deteriorate or even die, but it is gratifying to note that in only 7% in this series was there any severe disability. This included three patients who died from the effects of asthma, leaving some 4 to 5% still living but considerably disabled.

TABLE IX.—*Functional Assessment of Asthmatics at the End of 5–10 Years' Observation*

Grade:	1	2	3	4	5	Total
Onset	—	19	53	21	5	98
Peak	—	4	30	38	26	98
Follow-up at 5–10 years	45	43	3	1	6*	98

* 3 patients died from asthma.

Deaths

The deaths occurred, surprisingly enough, in three women.

Mrs. M. P., aged 35, died as a result of a sudden tension pneumothorax that developed during a severe bout of status asthmaticus (in 1950, before the days of corticosteroids).

Miss A. W. aged 68. Her asthma started late in life. This was eventually found to be connected with a polyarteritis nodosa, from which she died some years later.

Miss J. G., a frail and anxious spinster, began to suffer from asthma at 55; it was never well controlled, and she died from cor pulmonale at the age of 78.

Other authors, quoting figures from hospital practice, have also noted a good prognosis in asthma, although not as good as in this series (Table X). In both these series—Williams and Williams (1949) and McCracken (1950)—the periods of observation were over 7 to 12 years.

In my patients there was a difference in the prognosis of those whose asthma started in childhood (under 15)

TABLE X.—*Prognosis of Asthma—Other Series*

	No. of Attacks	Improved ++	Frequent Attacks	Death
Williams and Williams (1949)	20%	35%	28%	17%
McCracken (1950)	21%	54%	15%	10%
Average	66%		33%	

TABLE XI.—*Prognosis of Asthma Starting in Childhood—Other Series*

	No Attacks	Improved ++	Frequent Attacks	Death
Flensborg (1945)	41%	38%	16%	5%
Rackemann and Edwards (1952)	31%	40%	26%	3%
Average	75%		25%	

and in those who began attacks in adult life. In the former group the 5 to 10-year disability rate was only 5%, whereas in those whose asthma began in adult life the disability rate was as high as 18%.

Flensborg (1945) and Rackemann and Edwards (1952) also found a good prognosis in asthma in children (Table XI).

Comments

With an incidence of around 20 per 1,000 the average family doctor might expect to be kept busy caring for the 50-odd asthmatics in his practice, were it not for the apparently good prognosis and tendency towards a natural improvement.

A functional assessment of the 98 asthmatics in my practice has shown that in time as many as 90% cease to suffer major attacks. This pattern of improvement is undoubtedly part of the natural history of the condition, for the same trends are noted in the more severe types of asthma referred to consultants in hospitals. In reported series from hospitals between 66% and 75% of these more severely affected patients cease in time to be troubled by their asthma.

The importance and significance of appreciating this feature in the natural history of asthma are obvious. Our whole approach to asthma should focus on this aspect, and we should give our patients and their relatives a good and hopeful prognosis, and the management of our patients should be simple and be designed so that the attacks may be treated as they occur, with the efficient antispasmodics at our disposal, not forgetting the corticosteroids, which have greatly eased the management of severe cases. This non-specific approach must of course be supplemented by caring for various emotional, allergic, and other aspects of the individual patient.

While the course of most of these cases of asthma is towards a steady and natural improvement, it must be stressed that the situation in the 10% minority is potentially dangerous. It is in this small group that fatalities occur, especially in those over the age of 30, and it is these patients who will cause the family doctor and the consultant disproportionate anxieties.

Discussion

When one is dealing with a syndrome whose aetiology is uncertain, whose nomenclature is confusing, whose natural history is forgotten and unappreciated, and whose treatments are manifold, it is useful to start with a clean slate and take the syndrome as a whole and examine afresh possible clinical groupings and natural patterns of progress. This is what has been attempted in the present study in a general practice.

The family doctor is often bewildered by the many cases of "acute wheezy chests" in his practice. What are they? What is their outlook? What is their simplest form of management? Some answers have been suggested as a result of this study.

Three simple clinical groups were defined—wheezy children, asthmatics, and chronic bronchitics—and individual patients in the former two groups followed up for at least five years.

Fortunately, the course in the wheezy children and asthmatics was much better than expected. As the follow-up showed, 96% of wheezy children ceased to have trouble and in as many as 90% of asthmatics either their attacks stopped completely or they were little troubled by them. These figures may seem astonishingly good and other physicians may say, "But I'm sure I have many more bad cases." Unless accurate records are kept over long periods "impressions" and "opinions" are worthless. Inevitably it is the worst and most troublesome cases that are remembered. The asthmatics who proceed to status asthmaticus and the children who pass through the vulnerable years with many attacks of wheezing and other respiratory infections—these are the cases that are remembered rather than the many others that clear up uneventfully. These few problem patients cause us great anxieties and require very careful and individual care.

The history of wheezy children is one of natural and spontaneous improvement, and Goodall (1958) confirms this. The same tendency in asthma has also been noted by Flensborg (1945), Williams and Williams (1949), McCracken (1950), Rackemann and Edwards (1952), Williams *et al.* (1958), and Bruce Pearson (1958). This being so, management must be aimed at tiding our patients through the critical years by the safest and the simplest measures until the natural improvement occurs. When any "new" treatment is introduced and publicized it must be assessed carefully, using these natural patterns as baselines for comparison.

Summary

Considerable confusion exists over the causes, the significance, the course, and the management of acute wheezy attacks. The average G.P. seeing 40 to 50 such attacks each year is faced with many problems. This study has attempted to define simple clinical groups and to clarify the true natural history of these groups.

To carry out these aims 327 patients with such acute wheezy attacks in a practice of over 5,000 patients were observed and followed up for 5 to 10 years, from 1949 to 1958.

Three clinical groups were defined—wheezy children (126), asthmatics (98), and chronic bronchitics (121). Because of special problems a separate study is being made of the chronic bronchitics.

Wheezy Children.—There were 126 such children out of 797 at risk, a rate of 16%. In 87% the attacks first began before the age of 6. The peak periods for the attacks were in the first year of life and in the pre-school and early school periods. Single attacks were noted in 63% and only 8% had more than three attacks. At the end of the follow-up it was found that 87% had had no attacks for the previous three years and 9% were having very slight and insignificant attacks. Only 5% continued to wheeze after the age of 10.

Asthma.—The frequency was 98 cases out of 5,047 at risk—that is, 20 per 1,000 over five years. The annual incidence rate was around 11 per 1,000. In 53% the onset was in the first 10 years of life. In the history there were emotional illnesses in 24%, other allergies in 32%, a positive history in 15%, and an associated respiratory infection in 17%. At the peak (reached three to seven years from onset) there were 96% disabled. At the end of 5 to 10 years of observation the disability rate was only 10%, and in 90% the attacks had either ceased completely or caused very slight trouble. In those whose attacks began before the age of 15, 95% were free from trouble; in those whose

asthma began after the age of 15 there were 82% who were clear and not disabled from asthma.

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ORAL TREATMENT OF PERNICIOUS ANAEMIA: FURTHER STUDIES

BY

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During the past two and a half years the results have been published of 11 cases of pernicious anaemia treated with the oral vitamin-B_{12}–peptide complex, H.P.P./1, which was derived from a fermentation of a streptomyces mutant (Heathcote and Mooney, 1958a, 1958b; Mooney and Heathcote, 1960a). As a result of these findings we formulated a new hypothesis concerning the aetiology of pernicious anaemia—namely, that the disease is due to failure of gastric proteolysis and that intrinsic factor, as currently understood, does not exist. Table I summarizes the present state of 10 of these same patients. Case 39 (Mooney and Heathcote, 1960a) has been withdrawn from the series because he received, inadvertently, an injection of crystalline vitamin B_{12}. Nine of the remaining cases are still maintained on a daily dose of 10 μg. of vitamin B_{12} (78 μg. H.P.P./1) or less. Case 30, however (Mooney and Heathcote, 1960a), was barely maintained on a daily dose of 10 μg., and this has been increased to 20 μg. with satisfactory results (Table I). Haematological remission remains complete in all cases. No neurological complications have developed and there is no refractoriness. The duration of treatment now ranges from 476 to 1,409 days.

The main purpose of the present paper, however, is to describe the clinical results obtained in cases of pernicious anaemia, using a new peptide complex derived from fermentations of propionibacterium and to discuss these results and the others obtained from the streptomyces preparation in the light of present knowledge.

Properties of the Complex.—Six batches of a vitamin-B_{12}–peptide complex derived from fermentations of propionibacterium have been used in the clinical studies. These have been designated H.P.P./4, H.P.P./7, H.P.P./9, H.P.P./12, H.P.P./16, and H.P.P./17. The spectrophotometric curves of these preparations were similar to one another and to that of H.P.P./1 (Heathcote and Mooney, 1958a), having maxima at 277, 361, and 550 mμ. Amino-acid analysis of the preparations was also similar to that for H.P.P./1. The vitamin-B_{12}–peptide ratio of the batches varied, on a weight basis, from 1:3.7 to 1:7.1, thus showing that the preparation was not a chemical compound in the strict sense but rather a loose combination of peptide and vitamin which can occur in different proportions. Ultracentrifuge studies, carried out at the Microbiological Research Station, Porton, with one of these batches (H.P.P./7) have shown that it produces a single peak corresponding to a molecular weight of about 1,200–1,400—that is, of the same order as vitamin B_{12}. These and further ultracentrifuge studies at the Biochemical Laboratory, Cambridge, have clearly shown that there is no protein in the complex. Furthermore, the batches are dialysable.

Maturation of Megaloblasts.—It has previously been shown (Heathcote and Mooney, 1958a) that the vitamin-B_{12}–peptide complex H.P.P./1 matured megaloblasts *in vitro* in 18-hour cultures as rapidly as folic acid. This property is not shared by crystalline vitamin B_{12} alone, nor by gastric juice alone (Callender and Lajtha, 1951). Of the present vitamin-B_{12}–peptide batches only H.P.P./4 was tested in this way, but it also proved to be approximately as effective as folic acid in bringing about the maturation of megaloblasts.

Clinical Studies

Fourteen newly diagnosed uncomplicated cases of pernicious anaemia were treated with the propionibacterium complex. Three patients were males and 11 were females. The ages range from 36 to 80 years. Case 6A was used as a control, and Cases 11 and 14 in maximum response experiments. As all three of these received

TABLE I.—*Uncomplicated Cases of Pernicious Anaemia Treated Exclusively with Streptomyces Complex (H.P.P./1)*

Case No.*	Age	Sex	Duration Treatment (Days)	Vitamin-B_{12}–Peptide Complex (as μg. Vitamin B_{12})			Initial Blood Picture			Current Blood Picture			
				Total Dose	Mean Daily Dose	Current Maintenance Dose	Hb %	P.C.V. %	M.C.H.C. %	Hb %	P.C.V. %	M.C.H.C. %	Serum Vitamin B_{12} $\mu\mu$g./ml.
1	48	M	1,409	15,370	10·8	10	66	22	44	100	48	32·5	48
2	75	F	1,354	15,450	11·4	10	48	19	37	93	40	34	62
3	67	M	1,316	13,270	10·1	10	39	15	38	98	43	34	66
4	66	M	1,262	14,020	11·1	10	76	27	42	112	46	36·0	90
5	44	M	1,156	12,040	10·4	10	53	19	42	114	53	32	49
25	58	F	912	4,560	5·0	5	66	30	32	101	51	29·5	46
26	55	M	825	2,890	3·5	3·5	50	25	30	100	49	31·5	—
27	61	M	821	3,046	3·7	3·5	56	26	32	100	43	35·5	13
30	66	M	740	10,870	14·9	20·0	56	22	37	110	46·5	35·0	140
38	70	F	476	2,200	4·6	4·0	29	14	31	81	39·0	30·5	23
Average	61		1,026		8·6	9·0	54	22	36·5	101	44	34	60

* The numbers here refer to those same cases reported in the papers by Heathcote and Mooney (1958a) and Mooney and Heathcote (1960a).

crystalline vitamin B_{12}, either orally or parenterally, they are not included in Table II, but are described separately (see below).

Methods

The diagnosis of pernicious anaemia was confirmed by full examination of the peripheral blood, histamine alcohol test meal, and biopsy of the sternal marrow. Progress was assessed by packed cell volume (P.C.V.) readings (3,000 r.p.m. for 30 minutes) and by haemoglobin estimations (Hb 100% = 14.8 g./100 ml.).

The method of assay of serum vitamin B_{12} was essentially that described by Ross (1952), but using the "Z" strain of *Euglena gracilis* (Hutner *et al.*, 1956). The results obtained from 16 samples from normal controls ranged from 100 to 340 $\mu\mu$g./ml. of vitamin B_{12}, and the mean reading was 170 $\mu\mu$g./ml.

Dosage

For ease of administration of the minute doses of vitamin-B_{12}–peptide complex the material has always been mixed with mannitol. At the time of publication of our previous work it was being suggested in the literature (Chow *et al.*, 1956, 1958) that sorbitol in relatively large amounts (3–12 g.) aided the absorption of crystalline vitamin B_{12}. Although the amount of mannitol which we were giving per dose was extremely small (about 0.1 g.), it was decided to exclude the possibility of any improved absorptive effect which might be due to this. Accordingly, a portion of H.P.P./7 was admixed with lactose, and this preparation was coded H.P.P./7 L.B. It has since been shown, however, that sorbitol has no effect in aiding the absorption of crystalline vitamin B_{12} in pernicious anaemia (Herbert, 1958) or, indeed, even in normal subjects (Chalmers and Shinton, 1959). For all practical purposes, therefore, H.P.P./7 L.B. is the same as H.P.P./7 and, as will be seen from Case 16 (Table II), the response to the lactose-base preparation is equally good. No P.C.V. readings are available in this case, however, owing to the difficulty of obtaining blood by venepuncture.

For the sake of simplicity and consistency the doses of the different batches of the peptide complex are given in terms of the vitamin B_{12} content alone. Where crystalline vitamin B_{12} has been used it is mentioned specifically in the text.

In most cases a relatively high initial dose of H.P.P. was given for a short time. In this way the patients were exposed to minimum risk at a time when the blood picture was at its lowest. This initial dose was then followed by a low daily maintenance dose—usually the equivalent of 10 μg. of vitamin B_{12}—which was increased if necessary. No attempt was made to reduce the maintenance dose below 10 μg. daily in any of the cases.

Results

Control Case 6A.—A man aged 72 was given crystalline vitamin B_{12} (60 μg. a day) for 10 days. At the end of this period the blood count was unchanged, the haemoglobin remaining at 30% and the P.C.V. at 13% (Fig. 1). There was a trivial reticulocytosis which gave a maximum reading of 3.6% on the eighth day. On the 11th day 60 μg. of H.P.P./7 daily was given instead of the crystalline vitamin. A brisk reticulocytosis occurred which was maximum on the 17th day with a reading of 20.8%. By the 28th day—that is, when he had been on H.P.P./7 for 17 days — the haemoglobin had risen from 30% to 58%, and the P.C.V. from 13% to 28%.

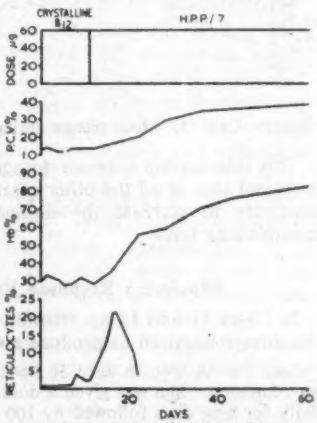

FIG. 1.—Control Case 6A.

Test Cases

The results obtained in the 11 test cases are summarized in Table II. At the time of writing four of these (Cases 8, 13, 16, and 22) were all satisfactorily maintained on daily doses of 10 μg., and the duration of treatment of these cases ranged from 900 to 1,077 days. Cases 31 and 45 were receiving 20 μg. a day. One patient (Case 17) died from cerebral haemorrhage on the 670th day, but up to the time of death she also was stabilized satisfactorily on a daily dose of 20 μg. Cases 10, 15, and 28 were being maintained on 30 μg. a day, and Case 12 was maintained on 40 μg. a day. Case 15 (Fig. 2) showed the typical behaviour of the blood picture during the period of stabilization. This patient was a woman aged 63. Initially she received 100 μg. of H.P.P./4 a day for eight days, which was followed by a daily maintenance dose of 15 μg. The blood picture began to deteriorate about the 62nd day (the average daily dose at this time was 26 μg.), and on the 146th day the daily dose was increased to 30 μg. This produced such a good response that on the 245th day the dose was reduced to 20 μg. a day. By the 300th day, however, it was apparent that this dosage was barely adequate for

TABLE II.—*Uncomplicated Cases of Pernicious Anaemia Treated Exclusively With the Propionibacterium Complex*

Case No.	Age	Sex	H.P.P. Batch	Duration Treatment (Days)	Vitamin-B_{12}-Peptide Complex (as μg. Vitamin B_{12})			Initial Blood Picture			Current Blood Picture			
					Total Dose	Mean Daily Dose	Current Maintenance Dose	Hb %	P.C.V. %	M.C.H.C. %	Hb %	P.C.V. %	M.C.H.C. %	Serum Vitamin B_{12} $\mu\mu$g./ml.
8	61	F	4	1,077	11,770	10·9	10	39	19	31	104	50	31	226
10	72	F	7	1,044	24,070	23·0	30	45	19	35	102	44	36	71
12	70	F	7	971	41,630	42·8	40	47	20	35	94	48	29	153
13	76	F	7	1,018	12,210	11·9	10	37	16	34	102	44	34	—
15	63	F	4	939	23,270	24·7	30	50	19	39	96	45	31	141
16	36	F	7 L.B.	933	10,020	10·7	10	63	—	—	100	—	—	—
17	76	F	7	652	12,780	19·8	20	22	14	24·5	76	39	29	72
22	80	F	9	900	9,190	10·2	10	38	16	35	91	40	34	38
28	66	M	12	779	19,930	27·4	30	45	19	35	88	40	33	50
31	68	M	17	740	10,750	14·5	20	69	31	33	105	42	37	10
45	37	F	16	293	5,980	20·4	20	57	26	32·5	106	46	34	23
Average	64	—	—	849	—	19·7	21·0	46	20	34	95	44	31·5	76

satisfactory maintenance, and it was then restored to 30 μg. The blood picture began to improve once more on this higher dosage, and has remained satisfactory after 939 days.

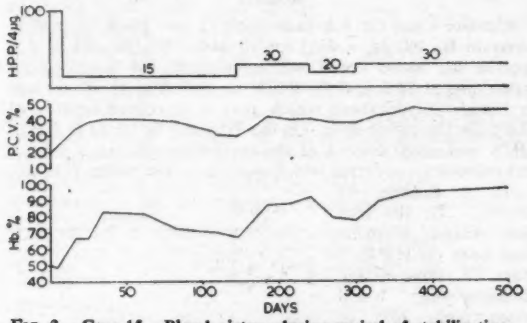

FIG. 2.—Case 15. Blood picture during period of stabilization.

This relationship between dosage and response (Fig. 2) is typical also of all the other cases in which it has been necessary to increase the dosage above the original maintenance level.

Maximum Response Experiments

In Cases 11 and 14 an attempt was made to discover the dosage required to produce a maximum response.

Case 11.—A woman aged 56 had a haemoglobin of 18% on admission. She was given a dose of 300 μg. of H.P.P./7 daily for nine days followed by 100 μg. a day for a further week, and the response was very good (Fig. 3). From the 17th to the 26th day inclusive the dose was reduced to 10 μg. daily. On the 27th day 500 μg. of parenteral vitamin B_{12} was administered, but no secondary reticulocytosis was observed. She has since been satisfactorily maintained on 10 μg. of H.P.P./7 a day for 1,031 days, and her haemoglobin at the time of writing was 91% and the P.C.V. 46%.

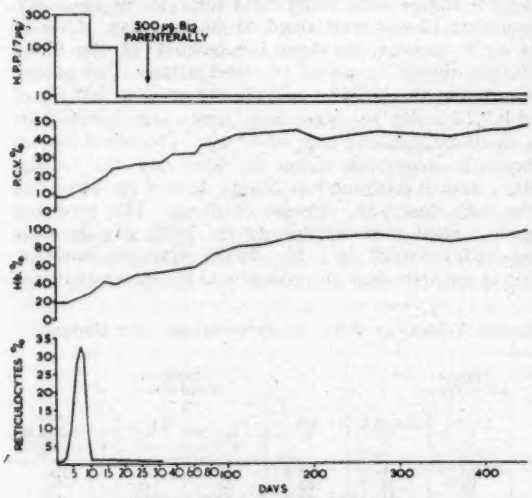

FIG. 3.—Blood picture of Case 11.

Case 14.—A woman aged 80 received 100 μg. of H.P.P./7 a day for 14 days. A slow response occurred. From the 15th to the 22nd day 10 μg. was given daily, and then 300 μg. daily from the 22nd to the 32nd day. A slight secondary reticulocyte response to the higher dosage then occurred, but a further 500 μg. of parenteral vitamin B_{12} given on the 39th day failed to produce any further reticulocytosis (Fig. 4). In spite of the apparently sluggish nature of the initial response to H.P.P./7, it would appear to have been maximal in her particular case. This patient was also satisfactorily maintained on 10 μg. a day, the haemoglobin being 95% and the P.C.V. 49% on the 1,104th day.

From the above results it would seem that a daily dose of 300 μg. of H.P.P./7 has been sufficient in each case to produce a maximum response.

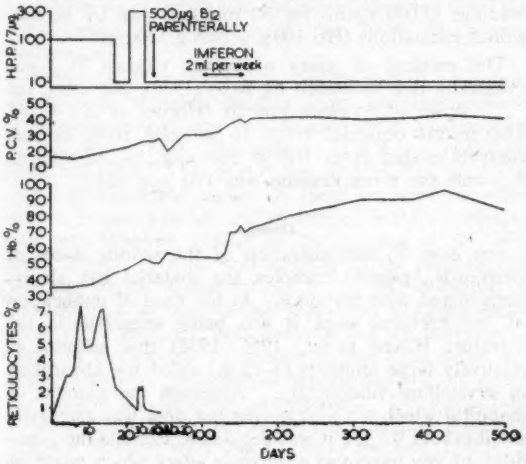

FIG. 4.—Blood picture of Case 14.

Discussion

Comparison with Crystalline Vitamin B_{12}.—The effect of oral crystalline vitamin B_{12} in pernicious anaemia has been studied extensively, and most of the work on this subject has been reviewed by Ungley (1951), by Brody *et al.* (1959), or by ourselves (Heathcote and Mooney, 1958a, 1958b). The differing schemes of dosage employed in the studies, however, make it difficult to summarize the findings in precise terms. There appears to be fairly general agreement, nevertheless, that daily doses of at least 100 μg. are required for maintenance in most cases (Hall, 1950; Chalmers and Shinton, 1958; Hemsted and Mills, 1958; Brody *et al.*, 1959), and some patients may require more. As the body requirements are about 1 μg. a day (Bethell *et al.*, 1948; Vilter, 1955; Pollycove and Apt, 1956) it can be inferred that the absorption of oral crystalline vitamin B_{12} into the haemopoietic system is probably on average no greater than 1% of a 100-μg. dose. This inference is supported by the work of Ungley (1951), who, from his series of 27 cases, concluded that absorption of the crystalline vitamin was rarely greater than 1%, and by Chalmers and Hall (1954), who found that an oral dose of 2,000 μg. was needed to produce the same effect as a parenteral dose of 20 μg.

In our experiments, maintenance over long periods has been possible in 10 cases on an average daily dose of 8.6 μg. of the streptomyces complex H.P.P./1. Similarly, 11 cases have been maintained on the propionibacterium complex on an average daily dose of 19.7 μg. These results, supported by the evidence from the control experiment described above and others reported elsewhere (Mooney and Heathcote, 1960a), demonstrate that both preparations are much more effective in the treatment of pernicious anaemia than crystalline vitamin B_{12} alone.

Serum Vitamin B_{12} Estimations.—Although we recognize that the serum vitamin B_{12} assay has a limited value in the study of pernicious anaemia, present knowledge hardly justifies placing its importance on a par with the actual clinical and haematological responses in assessing the efficacy of a particular preparation. Apart from the inherent limitations of microbiological assay—which are particularly great in the case of vitamin B_{12}—the actual interpretation of the results during H.P.P. therapy still remains largely a matter of conjecture (Mooney and Heathcote, 1960b). Nevertheless, it can be asserted with confidence, even now, that relatively low serum vitamin B_{12} levels on vitamin-B_{12}–peptide therapy are quite consistent with good clinical remission and absence of neurological complications and refractoriness (see below).

Refractoriness.—This has been constantly observed in cases of pernicious anaemia treated with all so-called purified intrinsic-factor preparations, and it may appear at any time between 3 and 48 months after the commencement of therapy (Blackburn *et al.*, 1955; Meulengracht, 1953; Nørregaard, 1955; Bastrup-Madsen, 1957; Schwartz *et al.*, 1957, 1958). Schwartz *et al.* (1958) reported that 11 out of 16 cases developed refractoriness after an average period of 18 months. In our series of 21 patients (Tables I and II) who have been treated exclusively with the H.P.P. preparations for an average period of over two years no case of refractoriness has occurred as yet.

Aetiology of Pernicious Anaemia

The premature conclusion, still open to dispute, that crystalline vitamin B_{12} is the extrinsic factor, and possibly the haemopoietic factor itself (Castle, 1953), has obstructed critical work on the aetiology of pernicious anaemia for several years, and has led to another possible error—namely, the belief that the missing gastric factor merely facilitates absorption of the crystalline vitamin. It is perhaps unfortunate, too, that the Schilling (1953) test—which has become the popular method for measuring the activity of the gastric factor—depends on these and certain other assumptions which have not yet been proved. We believe that the final solution to this problem will be reached, not by studying the behaviour of the vitamin in its unnatural crystalline form, but only by returning to the investigation of the behaviour of the naturally occurring—that is, protein-bound—form, under the influence of various gastric enzymes. This we have already discussed in our previous publications (Heathcote and Mooney, 1958a, 1958b).

Unpublished *in vitro* experiments which we have carried out with normal gastric-juice digests of both beef muscle and cheese have indicated that the vitamin is present after digestion in a dialysable form but still firmly bound to polypeptide. The vitamin-B_{12}–peptide complexes which we have described in this paper are more loosely complexed than those of the gastric-juice digests and probably simulate more closely the intestinal forms. This association between vitamin and peptide may be due to hydrogen-bonding, Van der Waal's forces, or some similar type of attachment common to polypeptide association phenomena; but, whatever the nature of the association between the vitamin and the peptide, there is no doubt that both solubility and clinical effectiveness are greatly increased when compared with the crystalline vitamin.

The mounting evidence that vitamin-B_{12}–peptide complexes are so highly efficacious in the oral treatment of pernicious anaemia enhances the view we expressed previously, that the disease is caused essentially by a failure of gastric proteolysis and that "intrinsic factor," as hitherto understood, does not exist. Furthermore, we believe that the evidence to date has failed to establish that crystalline vitamin B_{12} is either the extrinsic or the haemopoietic factor.

Summary

Our previous clinical studies in which we used a vitamin-B_{12}–peptide complex derived from *Streptomyces griseus* (H.P.P./1) have been extended to include cases treated with batches of a vitamin-B_{12}–peptide derived from fermentations of a species of *Propionibacterium*.

Ten patients receiving H.P.P./1 have now been maintained for an average period of 1,026 days on an average daily dose equivalent to 8.6 μg. of vitamin B_{12}.

Eleven patients receiving the propionibacterium peptide complex have been maintained for an average period of 849 days on an average daily dose equivalent to 19.7 μg. of vitamin B_{12}.

The superiority of the propionibacterium complex over crystalline vitamin B_{12} in the oral treatment of pernicious anaemia has been demonstrated in a controlled experiment, and daily doses of 300 μg. of vitamin B_{12} equivalent have given a maximum response in two other patients.

No refractoriness or neurological complications have developed and all patients remain in complete clinical remission.

It is again a pleasure to acknowledge the helpful co-operation we have received from Dr. E. T. Baker-Bates and Dr. G. M. S. Ryan. We are also indebted to Mr. J. J. H. Hastings for much constructive advice; to Mr. R. Goodey for serum vitamin B_{12} estimations; and to Miss J. Careswell and the staff of the St. Helens and Providence Hospital Laboratories for technical assistance. Finally we are grateful to the Biochemical Laboratory, Cambridge, and the Microbiological Establishment, Porton, for ultracentrifuge studies.

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PERNICIOUS ANAEMIA IN JAMAICA

BY

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Megaloblastic anaemias are common in tropical countries and usually have a background of nutritional deficiency. In Jamaica megaloblastic anaemia of infancy is extremely common (MacIver and Back, 1960a, 1960b), and is due to a nutritional deficiency of folic acid. On the other hand, megaloblastic anaemia of pregnancy is rather rare. In Trinidad, Habib (1960) has reported several cases of megaloblastic anaemia in adult males — strict Hindus — apparently due to a primary nutritional deficiency of vitamin B_{12}. Classical Addisonian pernicious anaemia is known to occur in the negro, but there is still some debate on its relative frequency in comparison with other races. It is well known that the incidence of pernicious anaemia varies widely among Caucasian races (Wintrobe, 1956), but it is still usually stated to be very rare in the negro when compared with the Caucasian (Kampmeier and Cameron, 1956; Wintrobe, 1956; Whitby and Britton, 1957). Although the relative frequency in the negro cannot be determined accurately at present, it is becoming increasingly evident that the incidence in this race is probably higher than was formerly thought.

The actual clinical appearance of pernicious anaemia probably depends upon several factors. These include the severity and duration of the gastric atrophic lesion, the dietary intake of vitamin B_{12} and folic acid, and conditions which may alter the need for the absorption and utilization of these vitamins. It seems likely that these predisposing causes may be encountered more frequently in tropical than in contemporary Western medicine. Further study and increased awareness may indeed show that the incidences of pernicious anaemia in the negro, and some, at any rate, of the Caucasian races, are comparable. The relative incidence in the negro may even be exaggerated by the present trend towards the production of multivitamin preparations by the drug houses and their almost faddist consumption by a sophisticated public in Western communities. This has probably tended to suppress the clinical emergence of classical pernicious anaemia in otherwise predisposed individuals in these areas.

The purpose of this paper is to review the individual data on 10 negro patients with pernicious anaemia admitted to the University College Hospital in Jamaica in the 30 months from January, 1958, to June, 1960, and to indicate the frequency with which this disease is encountered locally. The usually accepted diagnostic criteria were followed. All the patients showed a macrocytic anaemia, a megaloblastic marrow, a histamine-fast achlorhydria, and a satisfactory response to vitamin B_{12} therapy. In addition, the Schilling test was positive in seven patients. Gastric biopsy showed the characteristic atrophic lesion in the six patients on whom this test was carried out.

Methods

Schilling Test.—The fasting patient was given 0.5 μc of ^{60}Co or ^{58}Co-labelled vitamin B_{12} in 25 ml. of water. Twenty minutes later a light breakfast was given, and two hours later the oral dose of 1 mg. of non-radioactive vitamin B_{12} was given by parenteral injection. All urine passed in the next 24 hours was collected and the volume measured. A 200-ml. aliquot of the urine was concentrated by evaporation to rather less than 20 ml. and the final volume adjusted to 20 ml. The radioactivity in this concentrate was determined and compared with that of a standard prepared by making a 1 in 50 dilution from the original oral dose. A thallium-activated sodium iodide well crystal and Ecko ratemeter were used. The test was repeated giving 30 mg. of an intrinsic-factor preparation at the same time as the oral dose of radioactive vitamin B_{12}.

Gastric biopsies were carried out using the suction-operated intestinal biopsy capsule described by Crosby and Kugler (1957). Fundal biopsies were taken and correct positioning of the biopsy capsule was ensured by screening.

Clinical and Laboratory Findings

The clinical and laboratory findings are summarized in Tables I and II. The presenting symptoms were in most instances referable to the anaemia and/or the accompanying neurological lesions and did not differ significantly from those of patients described elsewhere. There were, however, a number of points in the history and clinical findings which appear to merit special mention. Anorexia, vomiting, and weight loss of varying severity were particularly common features, and were encountered in 7 of the 10 patients. The duration of these symptoms ranged from a few weeks to several months. Seven of our 10 patients presented neurological symptoms and showed clinical evidence of a peripheral neuritis. Five of these also had central cord involvement (Table II). Hepatomegaly of two fingerbreadths or more was found in eight patients. In Case 7 the liver was hard and irregular and non-tender: liver function was impaired, and the liver biopsy was consistent with a post-necrotic scarring. The liver-function tests in the other patients with hepatomegaly were within normal limits; and the hepatomegaly subsided gradually with treatment. Glossitis was found on examination or as a presenting symptom in five patients. Three cases showed a mild splenomegaly which rapidly subsided with treatment.

In seven patients stools were examined for fat to exclude steatorrhoea as a possible cause for the anaemia. This was normal in all instances except Case 1, in which it was raised slightly. However, the prompt and sustained response to vitamin B_{12} therapy alone in this patient, as in the others, makes this explanation unlikely. In the seven patients whose stools were examined for parasites the results were negative.

Discussion

In the tropics malnutrition, helminth infestation, and protozoal infections are often the commonest causes of community morbidity and mortality; and not uncommonly they constitute the essential background of a wide variety of disorders. In Jamaica helminth infestation and protozoal infections are becoming less common

and were found in none of our patients. However, an inadequate dietary intake which is low in fats and protein and relatively high in carbohydrate is still far from uncommon. It has been shown in Jamaica to be the common and possibly necessary background to a number of apparently unrelated disorders. These include the vomiting sickness of Jamaica (Stuart *et al.*, 1955), veno-occlusive disease of the liver (Stuart and Bras, 1957), and a number of neuropathies of at present undetermined aetiology (Cruickshank, 1961). More recently folic-acid-deficiency anaemias in malnourished infants have been demonstrated (MacIver and Back, 1960a, 1960b). However, other megaloblastic anaemias, such as those often found with sprue and other forms of malabsorption, with pregnancy, and with malnutrition, are uncommon.

TABLE I.—*Clinical Findings*

Case No.	Age	Sex	Presenting Symptoms	Duration	Weight Loss lb.	Weight Loss kg.	Liver (Finger-breadths)	Spleen	Glossitis	Peripheral Neuritis	Cord Involvement	Icterus
1	52	F	Soreness of tongue, nausea, vomiting, weight loss Weakness of legs, paraesthesia Swelling of ankles, exertional dyspnoea	2 years 6 months 2 years	18	8·2	3	+	+	+	+	–
2	53	M	Shortness of breath, palpitations on exertion, generalized weakness Weight loss	3 weeks 2 years	25	11·3	2	+	+	–	–	+
3	45	M	Palpitations, exertional dyspnoea Paraesthesiae	8 months 2 years	–		3	–	+	+	–	–
4	56	M	Loss of appetite, weight loss, sore tongue, salivation	2 years	15	6·8	2	–	+	–	–	–
5	46	F	Nausea, vomiting, weight loss Palpitations, exertional dyspnoea	2 ,, 6 months	40	18·1	2	+	–	+	–	–
6	50*	F	Numbness, paraesthesiae Unable to walk Loss of appetite, weight loss	6 ,, 3 ,, 12 ,,	+++*		2	–	–	+	+	–
7	46	F	Sore tongue, loss of appetite Drowsiness, disorientation	5 years 3 weeks	30	13·6	3	–	+	+	+	+
8	74	M	Weakness of legs, unsteadiness of gait	2 years	++*		–	–	–	+	+	–
9	45	M	Generalized weakness, paraesthesiae, difficulty in walking, exertional dyspnoea	3 months	+*		2	–	–	+	+	+
10	38	M	Palpitations, exertional dyspnoea, giddiness	4 weeks	–		–	–	–	–	–	–

* Amount uncertain.

TABLE II.—*Laboratory Investigations*

Case No.	Hb	R.B.C. (mil./c.mm.)	P.C.V. %	M.C.V. (Cubic Microns)	M.C.H.C. (%)	W.B.C. (per c.mm.)	Blood Film	Megaloblastic Marrow	Reticulocyte Count i. At Onset ii. Maximum Response	Schilling Test % Oral Dose of Radioactive B_{12} Excreted in Urine in 24 hr. i. Without Intrinsic Factor ii. After 30 mg. Intrinsic Factor	Histamine-fast Achlorhydria	Atrophic Gastritis on Gastric Biopsy
1	6·3 12·5	1·85 5·26	19 41	100 77	33 30	3,700 7,100	Anisocytosis Macrocytosis Poikilocytosis	+	1 27·1	1·4 6·6	+	Not done
2	4·9		16		30		Hypochromia Anisocytosis Macrocytosis	+	0·8 —	Not done	+	+
3	5·9 14	2·15 5·0	18 45	120 90	32 29	4,400 5,200	Macrocytosis Poikilocytosis Polychromasia	+	7·8 —	,, ,,	+	Not done
4	7·5 13·6	1·82 5·0	19 44	105	34 31	3,150 6,750	Macrocytosis Hypochromia Anisocytosis	+	0·4 28	0·2 20	+	+
5	3·2 12·2	1·32 5·26	12 43	92 82	27 29	3,250 7,600	Anisocytosis Poikilocytosis Polychromasia	+	3·0 21·5	0·7 7·1	+	+
6	8·4 14·7	2·2 4·8	27 45	120 100	31 31	2,200 4,850		+		0·53 18·3	+	+
7	5·2 12·9	1·86 4·30	16 42	88 98	32 31	3,750 12,000	Macrocytosis Poikilocytosis Anisocytosis	+	3·5 26·0	Not done	+	+
8	10·3		31		33	3,300 6,150	Anisocytosis Poikilocytosis	+		2·2 16·5	+	Not done
9	3·1 12·3		11		29	10,100	Macrocytosis Poikilocytosis Anisocytosis	+	3 25	0·42 14·9	+	,, ,,
10	4·9 12·0		15		32	3,600	Hypochromia Anisocytosis Poikilocytosis	+	0·1 20	1·75 10·3	+	+

It was tempting at first to assume that our cases were merely clinical variants of the nutritional macrocytic anaemia so commonly found in other tropical areas. It soon became evident, however, that there were no significant differences between the clinical and laboratory findings in our patients and their response to treatment when compared with patients with classical pernicious anaemia. Our findings also confirm those of Watson and Castle (1946), who have summarized and presented the evidence that the basic nutritional deficiency and essential clinical features in cases of nutritional macrocytic anaemia differ from those in Addisonian pernicious anaemia.

Anorexia, vomiting, vague abdominal pains, and sometimes considerable loss of weight were common findings in our patients. Although alimentary symptoms are not uncommon in classical pernicious anaemia it is perhaps unusual to find such marked loss of weight. In his original description Addison stressed this point and emphasized that "to the very last and after a sickness of perhaps several months' duration the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect." The severity of the weight loss in the patients presented here (Table I) was clearly a consequence of the degree and duration of the alimentary symptoms. It is also likely that anorexia would produce an earlier and more marked weight loss in individuals who have lived for a number of years on an inadequate or marginal diet than in better-nourished individuals in temperate climates. Medical advice may be also sought rather later in underdeveloped areas. Hicks and Leavell (1950) thought that the excessive loss of weight found in their negro patients with pernicious anaemia was really explained by the longer duration of the disease and associated anorexia.

Some consideration, however, of the possible role of malnutrition in the genesis of pernicious anaemia in Jamaica is inescapable. That pernicious anaemia is a deficiency disease is certain. The severity and duration of the gastric lesion is clearly the most important single factor that dictates its clinical appearance. It seems reasonable, however, that an inadequate dietary intake of vitamin B_{12} would tend to enhance the effects of this basic lesion. Infestation with *Diphyllobothrium latum* causes a pernicious type of anaemia presumably by producing a conditioned deficiency of vitamin B_{12}, and probably merely unmasks pernicious anaemia in predisposed individuals. Wokes (1954) studied vitamin B_{12} deficiency in vegans—that is, persons living on completely vegetarian diets without even milk, butter, cheese, or eggs. One had subacute combined degeneration of the spinal cord, which responded to treatment with vitamin B_{12} (Badenoch, 1954). The increase in the number of cases of pernicious anaemia seen in Europe during and immediately after the 1914–18 war suggests that economic and, most likely, dietary factors may be of considerable importance (McIntyre *et al.*, 1959). It has also been shown that a large number of new cases of pernicious anaemia appear during the late winter and spring months (Grönberg, 1946), again suggesting the possible effect of dietary factors.

There have been several reports of pernicious anaemia in the negro in his African homeland. Trowell (1951) described a case in a man in Uganda. Adams and Wilmot (1953), in a paper on megaloblastic anaemia of pregnancy, stated that they had seen one African woman in whom the clinical features were indistinguishable from those of pernicious anaemia. In neither of these cases were there any symptoms referable to the central nervous system. Woods and Rymer (1955) report a case of pernicious anaemia in an African Bantu woman with prominent neurological features. The patient's condition deteriorated during treatment with folic acid and improved markedly when vitamin B_{12} was administered. Adams (1957) described a case, confirmed by gastric biopsy and estimation of the level of vitamin B_{12} in the serum, in a Zulu male. Foy and Kondi (1958) also mentioned four cases of proved pernicious anaemia seen by them in East Africa in a four-year period. One of their patients had vague neurological symptoms. Metz *et al.* (1958) reported 10 unequivocal cases in the Bantu, and mentioned two further cases in an addendum. Nine of these patients were seen during a period of two and a half years. One case had subacute combined degeneration of the spinal cord.

It is interesting to note that 7 of our 10 patients presented evidence of peripheral neuritis, and in five of these there was also central cord involvement (Table I). Although slower than the haematological response the degree of improvement in these five patients was surprising and rewarding. Even the most severely incapacitated (Cases 1 and 6) were able to discard their sticks and wheelchairs and return to nearly normal physical activity in spite of some persisting evidence of posterior and lateral column damage. Reports from other tropical areas include that of Zimmermann and Dugger (1948) from Panama ; and it is probably of some relevance that 8 of the 10 patients reported by these workers were migrants from the West Indies.

Conclusions on the relative frequency of pernicious anaemia in the negro and white races have been drawn largely from clinical impressions and from analyses of hospital admissions. Friedlander (1934), in analysing 500 cases of pernicious anaemia admitted to hospital, found that only about 0.05% of all negroes admitted had pernicious anaemia, whereas 1.2% of all Scandinavians admitted suffered from the disease. Wintrobe (1956) found 33 cases of pernicious anaemia in negroes out of a total of 329 cases in a hospital where the ratio of white to coloured patients was about three to one. From an analysis in another hospital, where 45% of the patients are coloured, Kampmeier and Cameron (1956) concluded that the disease was about seven times as common in the white as in the negro. Schwartz and Gore (1943) gave a white-to-negro incidence of five to one.

There are a number of factors not considered in these and similar analyses. The first is the relationship to age. A number of studies have shown that the incidence of pernicious anaemia increases strikingly with age (Eason, 1920 ; Meulengracht, 1925). It is well known that the average age of hospital populations tends to be higher in the more highly developed communities. For this reason alone there may be a false indication of a higher incidence in these communities if reliance is placed solely on hospital statistics. Added to this there is the fact that in many tropical countries survival to the age at which pernicious anaemia is likely to appear may be relatively uncommon. Therefore analyses that do not take into consideration population density in various age-groups and comparative death rates in the populations under study may be incomplete because of the deaths of predisposed individuals from unrelated causes before pernicious anaemia is manifested by clinical symptoms.

Comparison of incidence in biracial communities may also be fallacious if access to hospital and opportunities for full clinical and laboratory assessment are more limited for the negro than for the white on account of local social or economic circumstances. The picture is further complicated by the difficulty of establishing complete racial purity in the modern West Indian or American negro. All of our patients presented essentially negroid characteristics; but it cannot be affirmed with any certainty that there had been no admixture of white, Chinese, or Indian blood. For practical purposes, however, it can be said that they were typical and representative of the negro in the West Indies to-day.

These are aspects of the disease that clearly require careful and detailed analysis and constant awareness of the tendency for preconceptions to persist as misconceptions. For the reasons stated comparison with incidence rates from other hospitals is likely to be unrewarding. In our hospital, however, it is certainly significant that all our patients were diagnosed in the period from January, 1958, to June, 1960, whereas this diagnosis had been made only once in the previous five years (in a white American female). It was during these two and a half years that particular attention was being directed towards the study of two disorders commonly seen in Jamaica, which show some features of pernicious anaemia. These are the megaloblastic anaemia of infancy, which has been shown to be due to a dietary insufficiency of folic acid (MacIver and Back, 1960a, 1960b), and an unusual neuropathy of unknown aetiology, the neurological features of which are very similar to those of subacute combined degeneration of the spinal cord (Cruickshank, 1961). We have thought that it is this detailed study and increased awareness of these and allied disorders that account for the increasing frequency with which the diagnosis is being made locally, and not an increasing incidence.

Summary

Clinical and laboratory details are given on 10 negro patients with pernicious anaemia admitted to the University College Hospital in Jamaica in the 30 months from January, 1958, to June, 1960. All showed the usual clinical and laboratory features of pernicious anaemia; and in the patients on whom these tests were carried out the Schilling test and gastric biopsy findings were characteristic. Anorexia and loss of weight were conspicuous features.

It is thought that the rarity of this disease in the negro has been overemphasized and that hospital statistics may be misleading in this respect.

The literature on pernicious anaemia in other parts of the tropics is briefly reviewed. There is evidence that, in addition to the basic gastric lesion, dietary and economic factors may play a part in the genesis of the disease.

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THE SYMPTOMS OF HYPERPARATHYROIDISM*

BY

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For practical purposes the presence of a complication is needed to call attention to the diagnosis of primary hyperparathyroidism, but, particularly in recent years, patients have been seen whose initial complaint has not been due to either of the well-known complications of kidney stone and bone disease.

The parathyroid glands were discovered in 1880 by Sandström in Sweden; their relation to the calcium level of the blood was demonstrated by MacCullum and Voegtlin (1908). Von Recklinghausen (1891) described the generalized bone disease of osteitis fibrosa cystica, and Askanazy (1904) found a parathyroid tumour in a patient dead from this disease. Later, enlargement of the parathyroid glands was also noted in rickets and osteomalacia (Erdheim, 1907, 1914), and it was assumed that the parathyroid tumours in von Recklinghausen's disease were secondary to the bone disease. Schlagenhaufer (1915), however, suggested that the reverse might be true, though it was not until July 30, 1925, that Mandl, in Vienna, explored a patient's neck, and with removal of a parathyroid tumour the bone condition improved (Mandl, 1926). Hyperparathyroidism was then considered to be synonymous with von Recklinghausen's disease of bone.

Albright *et al.* (1934) pointed out that renal stones were often found in patients with hyperparathyroidism (in 42 of 83 patients reviewed) and that the renal lesions could occur without the classical bone disease. Later it was also noted that osteoporosis might occur without bone cyst formation. Cope (1944) reviewed 78 cases and showed that, in fact, renal disease was more common than bone disease, a finding confirmed by a paper from the Mayo Clinic (Keating and Cook, 1945). Cope (1957) recorded clinical types of primary hyperparathyroidism as shown in Table I. It will be noted that one patient had neither bone disease nor renal stones.

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TABLE I.—*Clinical Types of Primary Hyperparathyroidism. 175 Patients at the Massachusetts General Hospital* (1932–57)

Complication		No.	Percentage
Bone disease	Classic	48	27
	Osteoporosis	7	4
	Osteoporosis and renal stones	30	17
No bone disease	Renal stones	81	52
	Peptic ulcer and renal stones	8	
	No renal stones	1	

69% with renal stones.

Presentations from Renal Stones and Bone Disease

The presentation leading to the diagnosis of primary hyperparathyroidism is most commonly due to renal stones, which give rise to pain or urinary infection, or symptoms from secondary impaired renal function or hypertension. Occasionally, nephrocalcinosis or the finding of kidney stones on incidental plain *x*-ray film may lead to investigation for this disease. Between 2 and 8% of renal-tract stones appear to be caused by hyperparathyroidism (Cope, 1957; Hodgkinson and Pyrah, 1958).

Bone disease consisting of osteoporosis (not just decalcification, as so often stated), with or without cysts and tumours, may be of varying degree. The early symptom may be indefinite pain, often attributed to "rheumatism," "arthritis," or "neuritis," and well described by Mandl's (1926) historic record of a Viennese street-car conductor. He wrote: "The present illness

FIG. 1.—Deformed hands of patient with hyperparathyroidism, showing beaking of thumbs and finger-tips.

began five years ago with a from day to day increasing tiredness and feeling of pain in the pelvis and lower extremities. The pains were increased by all bodily efforts, sneezing, coughing, defaecation, etc. In the course of months the suffering so increased that the patient had to be pensioned." These pains may disappear within hours of removal of the hyperfunctioning parathyroid tissue. A pathological fracture may occur, or bone deformities such as collapse of vertebrae leading to shortening in stature, "pigeon-breast" deformity of the chest, or alteration in the shape of the hands (Fig. 1). Tumours, particularly in the jaws, metacarpals and metatarsals, and ends of long bones, may be reported on as benign giant-cell tumours. Every epulis is not due to hyperparathyroidism, but this diagnosis must be considered with each, so that a presentation may result from a visit to a dental department.

Anaemia and leucopenia may occur as a result of marked fibrosis of the bone-marrow in hyperparathyroidism with bone disease, and anaemia is also frequent in the presence of complicating renal disease. The anaemia may respond to iron (Albright and Reifenstein, 1948).

Atypical Presentations

Albright noted that renal stones were common in patients with hyperparathyroidism and might occur in the absence of bone disease. Now patients with hyperparathyroidism are being recognized who present with symptoms other than those from renal stones or bone disease. Clinicians have for many years been aware of these other symptoms in patients presenting with renal stones or bone disease, but only recently have these become the clue to diagnosis and not a secondary clinical aid to diagnosis. It is the question of the other symptoms setting the doctor the task of investigating for hyperparathyroidism. Often the investigation may then reveal kidney stones or bone disease, but more and more patients are being diagnosed who have neither of these. It is remarkable, on reviewing the records of patients with proved hyperparathyroidism, how many had been to their doctors with suggestive symptoms, admittedly often vague, before, say, the attack of renal colic which had led to the diagnosis.

Cope (1957), for instance, has recorded the story of a New Yorker, aged 45, who felt lackadaisical and without his usual energy while performing a desk job in the Navy during the second world war. The patient ascribed this to the uprooting of his wartime job, but on return to his old life he continued to feel out of sorts. It was then noted that he had a prominent right thyroid lobe, and in 1946 a partial thyroidectomy was performed without the finding of any disorder of the thyroid gland. He was better for three months, but then lapsed into his state of lack of energy; all he wanted was to sit and do nothing. In 1949 he changed his doctor, who found nothing abnormal on physical examination. The examination, however, included the Sulkowitch test for calcium content of the urine, and this showed a raised concentration. The doctor then asked for tests of the fasting serum calcium and phosphate levels to be performed, and received the news that the calcium level was raised at 12 mg., with the phosphate at 2.5 mg./100 ml. That night the patient called him in with an attack of left-sided abdominal colic and later passed a stone. The diagnosis of hyperparathyroidism was confirmed by the removal of an adenoma, but would have been made in the absence of renal symptoms.

Fatigue appears to be one of the symptoms of hypercalcaemia, which is the cause of other symptoms from which hyperparathyroidism may be diagnosed. These include muscular weakness, hypotonia, bradycardia, lassitude, loss of appetite, chronic constipation, polyuria,

TABLE II.—*Symptoms of Hypercalcaemia*

Fatigue	Muscular weakness
Lassitude	Hypotonia
Headache	Bradycardia
Loss of appetite	Chronic constipation
Mental disturbance	
Keratitis	
Polyuria	Polydipsia

polydipsia, keratitis, headache, and mental disturbance (Table II). Dsypepsia, pancreatitis, and other endocrine disease may also lead to the diagnosis of hyperparathyroidism.

The clues to the diagnosis of hyperparathyroidism in 230 patients at the Massachusetts General Hospital are shown in Table III (Cope, 1960). 16% were not due to renal stones or bone disease, but this figure probably should be higher, since the series dates from 1932 and is weighted by the earlier emphasis on bone disease.

TABLE III.—*Clues to Diagnosis of Hyperparathyroidism. 230 Patients at the Massachusetts General Hospital* (1932–59)

Bone disease	63 (27%)	Hypertension	3 (1%)
Renal stones	130 (57%)	Mental disturbance	2 (1%)
Peptic ulcer	19 (8%)	C.N.S. signs	3 (1%)
Pancreatitis	4 (2%)	No symptoms	2 (1%)
Fatigue	4 (2%)		

Presentations from Hypercalcaemia

The symptoms of hypercalcaemia are mainly vague, as already outlined, and may suggest Addison's disease or, in the case of polyuria and polydipsia, diabetes insipidus. A typical history has been related by Albright and Reifenstein (1948). A woman of 59 was first seen with fatigue and sleeplessness. Two years later she was admitted to hospital for a mastoid operation, and it was noticed that she had a large fluid intake between 4 and 7 litres a day; the blood-pressure was 160/100. On investigation five years later for these symptoms, when tests for diabetes insipidus were negative, the serum calcium level was found to be 12.4 mg. and the serum phosphate 2.4 mg./100 ml. There was a normal I.V.P. and no bone disease was seen on *x*-ray examination. The kidney function was impaired, but this improved after the removal of a parathyroid adenoma. (This is the patient already noted in Table I without bone disease or renal stones.)

At the Massachusetts General Hospital I saw two patients in 1958 with mental disturbance and hyperparathyroidism. The first patient was an elderly man with a large head suggestive of arrested hydrocephalus. The psychiatrist thought that the large head suggested hyperparathyroidism and asked for a serum calcium determination. The level was raised, and later a parathyroid adenoma was removed; the patient's mental state improved. The same psychiatrist, a few months later, saw a young woman with an atypical psychosis, and, remembering the first patient, asked for a test of serum calcium, which was found to be raised. After further investigation a parathyroid adenoma was removed. This patient, who had neither bone disease nor renal stones, then became rational. Nielsen (1955), who first described psychic disturbances with hyperparathyroidism, has reviewed five patients whose psychic symptoms disappeared after parathyroidectomy. Occasionally acute hyperparathyroidism, with hypercalcaemia, may give rise to coma, vomiting, dehydration, high fever, and tachycardia (Mandl, 1947; Albright and Reifenstein, 1948). One sign of hypercalcaemia is band keratopathy where there is a grey, granular, and superficial opacity limited to the paralimbal region on either side of the cornea (Walsh and Howard, 1947; Cogan *et al.*, 1948).

Presentation from Peptic Ulceration

It is probable that peptic ulcer is clinically significant in hyperparathyroidism. Dyspepsia is common, and St. Goar (1957), who made the comment that hyperparathyroidism was a "disease of stones, bones and abdominal groans," found that 4 out of 45 patients (8.8%) had peptic ulcers, and 16 out of the 45 had gastro-intestinal symptoms (nausea, vomiting, anorexia, weight loss, abdominal pains, and constipation). At the Mayo Clinic 24% of patients with primary hyperparathyroidism had proved peptic ulceration, and more had symptoms suggestive of this (Lee *et al.*, 1955). Most of the ulcers are duodenal ulcers. The patients who should particularly be screened for hyperparathyroidism will be those with peptic ulcers and renal stones. Parathyroidectomy has been shown to promote healing of some of the ulcers.

A patient whose story is remarkable was a girl of 19 who was admitted to the Massachusetts General Hospital with a haematemesis requiring the transfusion of 1.5 litres of blood. A barium-meal examination showed a duodenal ulcer. The residents had been told of the association of peptic ulceration and hyperparathyroidism and urged to investigate all patients whose peptic ulcers were strange (thus a girl of 19 with a duodenal ulcer which bled sufficiently to require blood transfusion). In the ward, and on the first visit to the out-patient department, the serum calcium was normal, but at the next visit the determination was repeated. This time it was raised and she was readmitted for investigation. There was no bone disease or renal stones, but the biochemical findings favoured hyperparathyroidism. At operation Dr. Cope removed an early parathyroid carcinoma.

Presentations from Pancreatitis and Pancreatic Lithiasis

Nephrocalcinosis is a familiar complication of hyperparathyroidism, but only recently has pancreatic calcification and recurrent pancreatitis become recognized as another complication of this disease. Cope *et al.* (1957) reported two cases and reviewed five more from the literature. Their second patient was a woman of

FIG. 2.—Extensive calcification of the pancreas in patient with hyperparathyroidism. (By permission of Dr. A. W. Spence.)

62 with a three-year history of epigastric distress who was admitted with acute pancreatitis. Despite medical and surgical treatment she continued to have recurrent episodes of pancreatitis. On the fourth admission a serum calcium estimation was 14.4 mg./100 ml.—the estimation was made as a routine test, hypocalcaemia being so often a complication of acute pancreatitis. The raised serum calcium led to exploration of the neck, with the finding and removal of a parathyroid adenoma. After this she had no more symptoms suggestive of pancreatitis. Hoar and Gorlin (1958) have since reported a further example of hyperparathyroidism presenting with acute pancreatitis, and we have at present a patient at St. Bartholomew's Hospital in whom exploration has revealed a parathyroid tumour. Her pancreas shows extensive calcification (Fig. 2) and she has had, in retrospect, recurrent attacks of pancreatitis. Primary pancreatic lithiasis is a rare condition, but, when encountered, efforts should be made to investigate the patient for hyperparathyroidism, which is almost

certainly a more common cause of pancreatitis and pancreatic calcification than the few records would suggest.

Presentations from Other Endocrine Disease

Underdahl *et al.* (1953) published a paper entitled "Multiple Endocrine Adenomas: a Report of 8 Cases in which the Parathyroids, Pituitary and Pancreatic Islets were Involved." Besides their own patients they reviewed 14 more with tumours of two or three of these glands. Zollinger and Ellison (1955) described a syndrome with four main characteristics—gastric hypersecretion and hyperacidity, severe peptic ulceration (often atypical), and a non-insulin-producing islet-cell tumour of the pancreas. The tumours of the pancreas were often multiple and many were malignant. Up to date at least 75 cases showing the Zollinger–Ellison syndrome have been described, and about a quarter of these had other endocrine tumours, including tumours of the parathyroids. Thus patients with other endocrine disease may on investigation show hyperparathyroidism.

Cope *et al.* (1958) published a paper on a new form of parathyroid hyperplasia with enlargement of all four parathyroid glands which they called "primary chief-cell hyperplasia." Four of the 10 patients had tumours of the pancreas and pituitary gland. One of these was a woman of 46 who gave a history of renal colic in 1954, and two operations for severe peptic ulceration in 1954 and 1957. At the second operation a nodule was removed from the pancreas which proved histologically to be a non-insulin-producing islet-cell adenoma. Because of this the possibility of hyperparathyroidism was considered and diagnosed. At operation in 1958 four enlarged parathyroid glands were found and subtotally resected, the glands showing chief-cell hyperplasia.

Another of the patients, a man aged 45, had had three operations for severe peptic ulceration, after which he had a generalized convulsive attack and was readmitted with confusion, headache, and blurring of vision. There was a strong family history of peptic ulceration, and his daughter had had two islet-cell tumours of the pancreas removed in 1953. She also had a history of passing a few small stones in 1952, and was investigated for hyperparathyroidism, with the finding, at operation in 1953, of primary chief-cell hyperplasia of the parathyroids. Because of this the father was investigated for hyperparathyroidism, which was proved at operation in 1953. His bones showed osteoporosis, and he was a tense, gloomy individual. An *x*-ray examination showed enlargement of the sella turcica due to a chromophobe pituitary tumour, and later he underwent a total gastrectomy because of further haematemesis. At this operation no pancreatic tumour was discovered, though on his recent death the pancreas showed at least 10 small islet adenomas (Cope, 1960).

Summary

The symptoms of hyperparathyroidism have been outlined, with emphasis on those not due to renal stones or bone disease. Hyperparathyroidism is more common than supposed, and cases are being missed, even when some of the presentations mentioned are remembered.

Investigation for hyperparathyroidism because of "other symptoms" may reveal kidney stones or bone disease, which would later possibly have given symptoms themselves. In this case the diagnosis of hyperparathyroidism may only be delayed, but this will be after a longer period of ill-health and perhaps increasing irreversible damage. More and more cases, however, are being diagnosed without renal stones or bone disease, and more than 15% of patients with hyperparathyroidism are now being detected without these being the clue to diagnosis.

The atypical presentations may be from hypercalcaemia, when the symptoms are often vague—fatigue, weakness, loss of appetite, constipation, polyuria, polydipsia, headache, and mental disturbance—and from peptic ulceration, pancreatitis, and other endocrine disease.

The basis of this paper is the experience obtained during 16 months which I spent at the Massachusetts General Hospital and Harvard Medical School as a Nuffield Fellow working under Dr. Oliver Cope, to whom I should like to extend my thanks and admiration.

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"Considerable progress has been made [in the U.S.A.] in the campaign to abolish the performance of painful experiments on animals by schoolchildren. The *Ladies Home Journal*, a very influential periodical, published a strong article condemning these cruel experiments and this was backed up by the *New York Daily News*. A body called the 1960 Science Achievement Awards for Students, which is under the aegis of the National Science Teachers' Association, has announced that it will not in future give awards for projects involving animal suffering. The Maryland Society for Medical Research has restated its decision not to offer animals to schools for painful experiments. In order to provide science teachers with a practical alternative to cruel experiments the Animal Welfare Institute, ever practical, has published a booklet called *Humane Biology Projects*. It contains sections written by experts on practical work which can be done by schoolchildren in the fields of ecology and conservation, bacteriology, animal behaviour, genetics, botany and physiology without causing animals to suffer." (*Annual Report and Accounts, July 1, 1959, to June 30, 1960*, Universities Federation for Animal Welfare.)

CARDIAC LESIONS IN REITER'S DISEASE

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Reiter's disease is a condition of unknown aetiology and in its generally recognized form is a triad consisting of urethritis, arthritis, and conjunctivitis. With increasing knowledge a number of characteristic though less constant features have been added to the clinical picture. However, many patients show only two of the cardinal features (commonly urethritis and arthritis), but the subsequent course is similar to the fully developed condition, and it is generally assumed that these are variants of a single disease entity. The condition may follow bacillary dysenteries, non-specific diarrhoea, or venereally acquired urethritis, and it most commonly affects young men. Its outstanding feature is acute arthritis, which usually involves several joints and may show a rapid evolution ; it has thus some resemblance to rheumatic fever, and this had led investigators to search for cardiac lesions.

Literature

In the older literature endocarditis was freely diagnosed on finding systolic murmurs and sometimes vague precordial discomfort soon after the onset of Reiter's disease (Stettner, 1917 ; Sick, 1918). There was no follow-up of these cases and the clinical evidence does not justify the claims made. Later some clinicians used electrocardiography as a routine investigation in Reiter's disease, and abnormal tracings were reported in a fairly high proportion of cases (Master and Jaffe, 1934 ; Gadrat and Morel, 1935 ; Candel and Wheelock, 1945 ; Feiring, 1946 ; Warthin, 1948 ; Lövgren and Masreliez, 1949 ; Shapiro *et al.*, 1949 ; Trier, 1950 ; Weinberger *et al.*, 1952 ; Mayne, 1955). The most constant finding was a prolonged P–R interval and sometimes there was a flattening of the T wave. No mention of symptoms or signs attributable to the heart was made in these cases. In the majority the changes were noticed in the first weeks after the onset of Reiter's disease ; in some the electrocardiographic abnormalities disappeared after a few weeks, in others they persisted for longer periods, but owing to the relatively brief observation time no definite conclusions could be drawn. Abnormal cardiac signs and symptoms, in addition to electrocardiographic ones, were described by several authors.

Bang (1940) reported six cases of what he called "gonorrhoeal myocarditis" ; however, the primary condition in five of them conforms to the classical picture of Reiter's disease. One of these patients had a pericardial type of pain and another had angina pectoris. The electrocardiograms showed prolonged P–R intervals, incomplete bundle-branch block, and flat or negative T waves. Films of the heart were normal and no significant murmurs were heard. Beiglböck (1943) diagnosed "mild mitral valve involvement" in one patient ; unfortunately, no details were given. Schuermann (1943) described three cases of "endocarditis" developing early in Reiter's disease and based his diagnosis on finding systolic murmurs and electrocardiographic changes which included flat T waves and slightly prolonged P–R intervals. Paronen (1948) studied 344 post-dysenteric cases of Reiter's disease in Finland during the second world war and found that 23 developed cardiac abnormalities : 7 had clinical pericarditis and 16 showed electrocardiographic changes only, which consisted of prolonged P–R interval, widened QRS complex, elevated ST segment, and flattened T waves. Owing to the circumstances of war, facilities for follow-up studies were limited, but it was noted that the pericarditis recurred in one patient some years later after he developed a further attack of Reiter's disease.

Csonka and Oates (1957) described three cases of pericarditis which developed during the course of venereally acquired Reiter's disease and noted electrocardiographic changes similar to those previously described. These patients have been closely observed since. One patient suffered a second attack of Reiter's disease with electrocardiographic evidence of transient myocarditis. The second patient had further episodes of conjunctivitis and experienced a mild attack of pericarditis three years after the first one. The third patient developed aortic incompetence and is fully described below (Case 1). Two additional cases, in which aortic incompetence developed in the course of Reiter's disease, are recorded. A fourth case, that of a woman with valvular lesions who came to necropsy, is also presented as she had several features in common with other patients ; there is, however, not sufficient evidence to diagnose Reiter's disease in this case.

Case 1

A West Indian developed non-gonococcal urethritis in 1955 at the age of 38. He gave a history of gonorrhoea in 1946, but no history of rheumatic fever or syphilis. The urethritis was followed 10 days later by arthritis involving joints of arms and legs, plantar fasciitis, and swelling of the Achilles tendons. The temperature was raised to 100° F. (37.8° C.) during the first week. A month later a mild conjunctivitis developed, and subsided in a few days. At about the same time the patient complained of central chest pain and a pericardial friction rub was heard. There was also a harsh systolic murmur at the apex. The apex beat was displaced to the left (5 in. (12.5 cm.) in the fifth space). The blood-pressure was 150/100. The electrocardiogram showed a prolonged P–R interval of 0.28 second and minor ST elevation in V_1–V_4. A chest *x*-ray film showed an enlargement of the heart due to prominence of the left ventricle (transverse diameter was 153 mm.). The affected joints and the spine were radiologically normal. Erythrocyte sedimentation rate (Westergren) was 80 mm./hour, the haemoglobin and blood count were normal. Wassermann and Kahn reactions were negative, the gonococcal fixation reaction was strongly positive. Treatment with oxytetracycline and salicylates was ineffective ; fever therapy with intravenous *Escherichia coli* vaccine was then tried with symptomatic improvement of the joints.

He was discharged from hospital three months after admission and resumed work as a porter a month later. He kept well until August, 1956, when he contracted gonorrhoea which responded to penicillin but was followed by non-specific urethritis ; two weeks later he complained of pain in both feet and lower back which lasted several months.

He recovered eventually and was back at work until in September, 1957, when there was a recurrence of polyarthritis, which responded to prednisone. He resumed work but has had several mild recurrences in the peripheral joints since. At an assessment in September, 1959, he felt reasonably fit and was able to manage heavy work without dyspnoea. The erythrocyte sedimentation rate was 23 mm./hour, and there was a slight swelling of the left knee, left ankle, and several interphalangeal joints. The blood-pressure was 160/96. The apex beat was displaced to the left (5½ in. (14 cm.) in the fifth space) and of left ventricular type. There was still an apical systolic murmur to be heard and, in addition, a soft blowing early diastolic murmur at the left sternal edge. On screening, a moderate left ventricular enlargement with diffuse dilatation of the aorta was seen. The E.C.G. showed little change from the first one taken four years before (Fig. 1). Serological tests for syphilis, which included the standard Wassermann and the treponemal immobilization test, were all negative. There were no L.E. cells in the peripheral blood; the differential agglutination test and latex fixation test were negative.

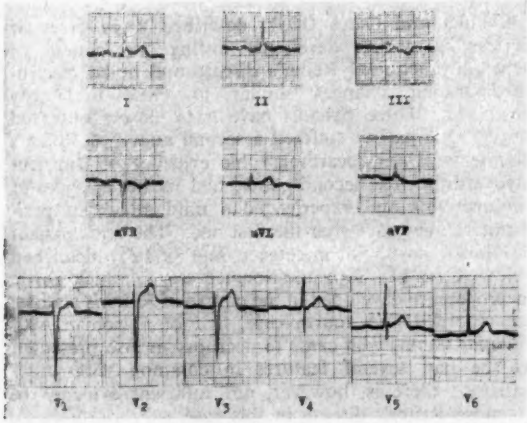

FIG. 1.—Case 1. Electrocardiogram showing P–R interval of 0.24 second and ST elevation in leads I, aVL, V_1, V_2, and V_4.

Case 2

In 1940, at the age of 27, the patient contracted gonorrhoea from his wife, and this was followed by non-gonococcal urethritis. A few days later painful swelling of several toes occurred; this subsided after a few weeks. He joined the Army and remained fit until 1945, when he developed arthritis in both ankles, low backache, plantar fasciitis, Achilles tendinitis, and bilateral iritis. Because of his illness he was invalided out of the Army soon afterwards and no abnormality of the cardiovascular system was recorded. He resumed his old occupation as a baker but found it difficult to keep working because of recurring pains in the joints of the legs, and backache. In 1950 he complained of central chest pain, but this was not investigated. In 1955–6 two iridectomies were performed; these were followed by cataract, which reduced his vision severely and he had to give up work. Since then there have been further attacks of iritis but no joint pain or swelling. For the past year he has noticed shortness of breath and palpitation on exertion.

There was no history of rheumatic fever or syphilis. On examination in July, 1959, he was found to have aortic incompetence. The blood-pressure was 170/50 and capillary pulsation in the fingers was present. The apex beat was displaced to the left (5½ in. (14 cm.) in the fifth space) and of left ventricular type; there was a soft systolic murmur and a loud blowing diastolic murmur maximal at the left sternal edge (Fig. 2). The peripheral joints and the spine were clinically normal. Vision was extremely poor and the patient could count fingers only with difficulty.

Investigations. — E.S.R. (Westergren) 33 mm./hour. Haemoglobin and blood count were normal. No L.E. cells were seen in the peripheral blood. The anti-streptolysin titre was 100 units/ml. Serological tests for syphilis were negative, and included the standard Wassermann and treponemal immobilization test. A chest *x*-ray film showed some left ventricular enlargement with a moderately prominent aortic arch. The transverse diameter in 1951 was 135 mm.; this had increased to 170 mm. in 1959. On screening the appearances were those of aortic regurgitation. In the electrocardiogram the P–R interval was 0.28 second. *X*-ray films of the sacro-iliac joints showed bony subarticular sclerosis and narrowing of joint spaces; no changes were visible in the lumbar or thoracic spine. There was a small calcaneal spur on the left side.

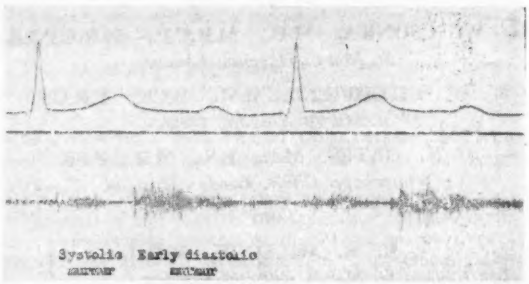

FIG. 2.—Case 2. Phonocardiogram showing systolic ejection murmur and diminuendo diastolic murmur of aortic incompetence.

He was treated with rest in bed and prednisone, starting with 40 mg. daily and reducing to half this dosage after one week. He was discharged on this dose after one month in hospital. During this time the sedimentation rate became normal. An electrocardiogram taken six months later showed a P–R interval of 0.20 second. At the time of writing he was quite well and complained only of occasional tiredness.

Case 3

A man aged 53 was first referred to one of us in February, 1957, while under observation for aortic incompetence, which was suspected of being syphilitic in spite of negative serum tests with lipoidal antigens. He gave a history of having contracted gonorrhoea in 1927 at the age of 30. In 1935 he developed arthritis of the feet and was in hospital for nine months. Later a low-grade non-gonococcal urethritis was found. Wassermann, Kahn, and gonococcal fixation tests were negative. In 1936 chronic prostatitis was diagnosed and he received intermittent treatment for a year. In 1940 he developed bilateral iritis, and there were several recurrences in the following years. In 1941 he attended with cystitis; no gonococci were found. In 1956 he noticed increasing shortness of breath.

A year later there was no history of rheumatic fever or syphilis. On examination (February, 1957) he was found to have aortic incompetence. The blood-pressure was 180/60 and there was a waterhammer pulse. On auscultation a soft diastolic murmur was heard at both sternal margins. *X*-ray examination of the heart showed some left ventricular hypertrophy (transverse diameter 140 mm.) but no calcification of the aorta. The only abnormality of the electrocardiogram was a prolonged P–R interval of 0.24 second. There was no urethral discharge and the urine and prostatic secretions were free from pus. The eyes showed multiple opacities in both anterior chambers. Both feet were deformed, with marked lateral deviation of the toes. *X*-ray examination of the feet showed disorganization of the metatarsophalangeal joints, with subluxation and lateral deviation of the phalanges as well as bilateral calcaneal spurs. *X*-ray examination of the spine showed some sclerosis of both sacro-iliac joints (Figs. 3–5). The Wassermann and treponemal immobilization tests were negative. On

examination of the cerebrospinal fluid the findings were normal (no cells, protein 40 mg./100 ml., Lange 0000000000, Wassermann negative). E.S.R. (Westergren) 36 mm./hour. Haemoglobin and white-cell count were normal.

Between February, 1957, and December, 1959, the patient had two further attacks of iritis, otherwise his general condition remained unchanged. In December, 1959, a further cardiac assessment was made, when it was felt that there were no symptoms referable to the cardiovascular system. E.S.R. was 6 mm./hour. Peripheral signs of aortic incompetence were marked. The blood-pressure was 150/40. The other findings were similar to those of 1957 except for the electrocardiogram, which now showed evidence of left ventricular hypertrophy and a P–R interval of 0.42 second.

FIG. 3.—Case 3. Disorganization of metatarsophalangeal joints with lateral deviation of the toes.

FIG. 4.—Case 3. Calcaneal spurs.

No specific treatment has been given to this patient, and his physical condition has remained virtually unchanged during the three years of observation.

A further case, that of a woman who came to necropsy, is described below, though the diagnosis of Reiter's disease could not be made with certainty. The aetiology of the cardiovascular lesion which led to her death was puzzling, and it was only in retrospect that the possibility of Reiter's disease suggested itself.

Case 4

A married woman developed iritis of the left eye in 1943 at the age of 37. Right iritis followed in 1947; since then she had noticed dyspnoea and palpitation on moderate exertion. In 1951 aortic regurgitation was diagnosed. Earlier in that year painful swelling of both knees and ankles occurred, lasting for a few weeks. She was admitted to St. Mary's Hospital for investigation. The pulse was of waterhammer quality; the blood-pressure 140/40. The cardiac impulse was 5¼ in. (13.3 cm.) out in the left fifth space. A grade 3 systolic murmur was maximal over the aortic area and there was a faint early diastolic murmur down the left side of the sternum. No signs of cardiac failure were found. Clinically, no abnormalities of the peripheral joints or spine were noted. There was a low-grade fever of 99° F. (37.2° C.). No history of rheumatic fever, chorea, or syphilis was obtained.

Investigations.—Haemoglobin 90%; white blood count 12,000, with 8,650 neutrophils; E.S.R. 48 mm./hour. (Westergren); blood Wassermann reaction and Kahn test were negative. The electrocardiogram showed sinus rhythm, a P–R interval of 0.24 second, and a Q–T interval of 0.40 second. There was a slight ST depression in the left

FIG. 5.—Case 3. Sclerosis of the sacro-iliac joints.

ventricular leads, thought to be an effect of digitalis. Chest *x*-ray examination showed some left ventricular enlargement with a transverse diameter of 150 mm. Muscle biopsy gave no evidence of polyarteritis nodosa.

Her dyspnoea improved after rest and the administration of digitalis. Repeated attacks of iritis caused progressive loss of vision, despite a right iridectomy in 1954. The E.S.R. remained slightly raised.

In 1956 attacks of nocturnal dyspnoea necessitated readmission to hospital. Auricular fibrillation was now present and the jugular venous pressure was raised. The cardiac enlargement was more marked and there were numerous crepitations at the left base. A to-and-fro aortic murmur was present. The E.C.G. showed auricular fibrillation. On the *x*-ray film of the chest the transverse diameter of the heart measured 170 mm. and both lung fields showed widespread congestive changes.

Cardiac failure responded slowly and incompletely to rest, digitalis, mersalyl, and salt restriction. She quickly relapsed after discharge from hospital and died on April 19, 1956, in intractable cardiac failure, hastened by the occurrence of pulmonary emboli.

Post-mortem Findings

Post-mortem examination by Dr. E. A. Wright at St. Mary's Hospital showed evidence of long-standing congestive heart failure with terminal pulmonary infarction.

Gross Appearances. — *Externally* deceased showed moderate pitting oedema of the ankles and lumbar pad. *Internally* there was a recent pericarditis with fibrinous exudate over the epicardium. The heart was greatly enlarged (565 g.), owing mainly to hypertrophy of the left ventricle. The thickening of the tricuspid valve cusps was considered to be within normal limits. The commissures of the pulmonary valve cusps were separated respectively 1, 0.5, and 0.5 mm. The endocardium of the left atrium was opaque and thickened. The mitral valve cusps were slightly thickened and the cordae tendinae were moderately shortened, thickened, and matted together. There was considerable endocardial thickening over the apices of the papillary muscles. The mitral valve was, however, not

stenosed, although it was thought that there was a slight degree of incompetence. The aortic valve was incompetent to a marked degree, its cusps being elongated, and showed thickened, rolled, cord-like edges which prevented their approximation. The commissures were, however, neither separated nor fused. The coronary arteries were free of disease. The thoracic aorta showed five distinct scarred areas up to 1 cm. diameter where the wall was thinned, stretched, and pearly grey in colour. In addition there was extensive superficial irregularity indiscriminately mixed with superficial plaques of fatty atheroma. The pulmonary artery was also superficially scarred but atheroma was not present. The lungs were congested and showed three small branches of the pulmonary arteries occluded with emboli. The embolus in the right lower lobe was associated with a recent infarct, 5 cm. in diameter, estimated to be 2 to 3 days old. The liver and kidneys were congested. The spleen (360 g.) was enlarged and showed a firm pulp. The right femur showed red marrow throughout its length. The uterine cervix was eroded. There were no significant lesions in any of the other organs.

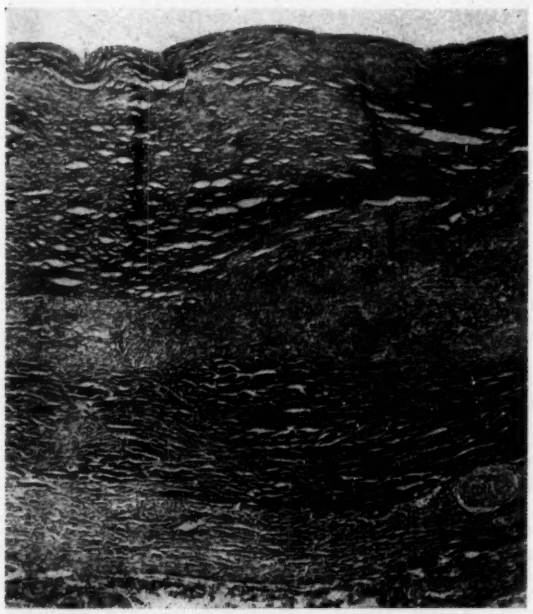

FIG. 6.—Case 4. Low-power view (×50) of thoracic aorta stained with haematoxylin and eosin. The thickening of the intima and adventitia and the irregular thinning of the media are seen.

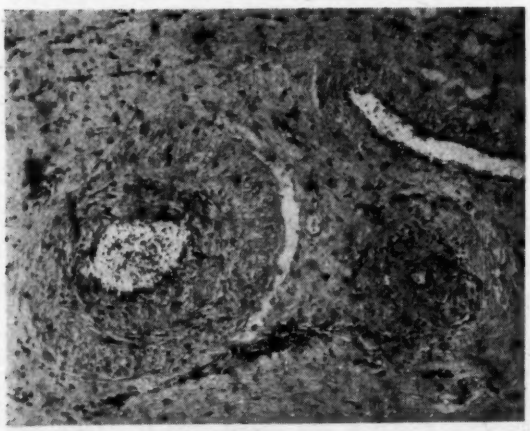

FIG. 7.—Case 4. High-power view (×78) of vessels from adventitia of thoracic aorta stained with haematoxylin and eosin, showing endarteritis and lymphocytic infiltration.

Microscopical Appearances.—The *aorta* (Figs. 6 and 7) showed intimal thickening and moderate atheroma, which was slightly calcified in places. The media was greatly thinned in the scarred areas and showed vascularization. The adventitia was greatly thickened with fibrosis and showed many small arterioles which were narrowed by endarteritis. In addition there were many areas of cellular infiltration, sometimes situated perivascularly. The cells were mainly lymphocytes, but there were also small numbers of plasma cells and occasional macrophage cells. The *left atrium* showed endocardial thickening with fibrous tissue which in places was 1 mm. thick. The myocardium showed slight diffuse replacement with fibrous tissue. The *cervix* showed a few mucous cysts and an erosion. The erosion was markedly vascular, but the subjacent infiltration with chronic inflammatory cells was slight. Sections of other organs confirmed the macroscopic findings.

Comment.—The macroscopic and microscopical lesions found in the cardiovascular system of this case show some features that are usually ascribed to the late effects both of syphilis and of rheumatic endocarditis. However, it seems probable that these changes are the late result of some other widespread cardiovascular disease.

Discussion

The incidence of serious valvular lesion of the heart arising in Reiter's disease is probably very low. Thus the possibility of this complication was suggested as early as 1917 by Stettner, yet no case with unequivocal valvular lesion has been reported to date. It is possible that such cases have been missed, as commonly the observation period was short and the subsequent cardiac status remained unknown. It is also likely that a patient with arthritis and valvular lesion of the heart is diagnosed as having rheumatic fever because the less prominent and often fugitive involvement of the urethra and the eyes is not inquired into.

Three patients previously described as having sustained attacks of pericarditis have been followed up by us and all have shown evidence clinically or electrocardiographically of further episodes of cardiac involvement. In one of the patients incompetence of the aortic valves has developed, and that this is not a chance finding is supported by the description of two further cases. The three men with aortic incompetence were found in a long-term study of 215 patients with Reiter's disease. The experience in ankylosing spondylitis is similar in this respect, as the two patients with aortic incompetence reported by Ansell *et al.* (1958) were diagnosed during a careful survey of 222 patients with classical ankylosing spondylitis. There is also similarity in the histological features of the cardiac lesions in Case 4 and those described in ankylosing spondylitis (Bauer *et al.*, 1951 ; Ansell *et al.*, 1958).

The difficulty in distinguishing the aortic lesions of ankylosing spondylitis from those caused by syphilis has been noted by several authors. In Reiter's disease, which may be closely linked with venereal infection, the exclusion of concomitant syphilis as an aetiological factor in the development of aortic lesions is clearly of importance. The recent advent of truly specific treponemal serological tests has made this task much easier, and it was possible to take full advantage of this in three of our patients.

It is noteworthy that iritis was present in three of our four patients, whereas in our experience of 215 consecutive cases of Reiter's disease it was found only in 17%. Radiographic evidence of sacro-iliitis was seen in two of the three male patients, but there was no suggestion of spinal involvement as found in classical ankylosing spondylitis.

The nature of the cardiovascular lesions described here is unknown, and, although potentially dangerous, they have not caused serious functional disability in three of the patients. One patient received prednisone therapy, during which time the erythrocyte sedimentation rate became normal, as did the previously prolonged P–R interval.

Summary

Three cases of Reiter's disease with aortic incompetence are described. The aortic lesion is believed to have developed during the course of Reiter's disease. This complication appears to be unusual, as no similar cases have been reported in the literature.

A fourth patient, a woman with iritis, transient arthritis, cervicitis, and aortic incompetence, came to necropsy and is also recorded, though the diagnosis of Reiter's disease could not be made with certainty.

A characteristic feature of the electrocardiogram was a prolonged P–R interval present at some time in all our patients.

The nature of the cardiac lesion is unknown.

Similar cardiac lesions have been described in a number of patients with ankylosing spondylitis, and this could give rise to some diagnostic difficulties.

We thank Dr. A. E. Wilkinson, director of the V.D. Reference Laboratory (M.R.C.), for carrying out the serological tests for syphilis. One of us (G. W. C.) received a grant from the U.S. Public Health Service under the aegis of the Medical Research Council Working Party on Non-Specific Urethritis.

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The *Hospitals Year Book, 1961*, has recently been published by the Institute of Hospital Administrators. The main change in this edition is that the directory of Northern Ireland Hospital Services has been revised and expanded to bring the information given about hospital management committees and their hospitals in Northern Ireland into line with that given in the sections for Great Britain. The *Year Book* is obtainable from the Institute, at 75 Portland Place, London W.1, price 59s. 6d., postage 2s. 3d.

FATAL DIABETIC KETOSIS

BY

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There has been a marked reduction in the number of deaths from diabetic ketosis during the past 20 years. The low mortality of between 2 and 5%, in a series reported by Harwood (1951) and Joslin *et al.* (1959), has led to a general belief that fatal ketosis is now exceptional, and that when it occurs it is due to faulty treatment. However, mortality rates of about 15% reported from Melbourne (Greenaway and Read, 1958) and Cincinnati (Skillman *et al.*, 1958) do not support this. The absence of a published series from hospitals in this country in recent years has prompted the present study, in which 19 fatal cases are described.

Material

The results of treatment of 160 episodes of severe ketosis are considered. These were consecutive admissions to the General Hospital, Birmingham, in the five years between January, 1955, and December, 1959, and were contributed by 122 patients (2 patients had ketosis five times, 2 four times, 4 three times, and 16 twice). Fourteen of the patients had ketosis more than once in the same year. We have included in the series only those patients who showed obvious and visible air hunger on admission to hospital, for at this stage it can safely be claimed that ketosis has become severe and that coma is impending. The level of plasma bicarbonate was not regarded as a sufficiently reliable guide to be used as a criterion of clinical severity (Owens and Rockwern, 1939 ; Collen, 1942 ; Black and Malins, 1949 ; Harwood, 1951 ; Hudson *et al.*, 1960).

Results

Age, Sex, and Seasonal Incidence.—There were 60 episodes in males and 100 in females ; the series does not include those in children under 10. The Table shows the number of episodes in each 10-year age-group for both sexes, and Fig. 1 compares the incidence of ketosis in males and females with the prevalence of diabetes in all patients attending the hospital diabetic clinic. Thus the series is of comparable age and sex composition to those of Harwood (1951) and Cohen *et al.* (1960), but the mean age of admission is 10 years above that of the Joslin Clinic series (Joslin *et al.*, 1959). The significant excess in the incidence of ketosis in adolescent girls has been found before (Joslin *et al.*, 1937 ; Owens and Rockwern, 1939). Unlike the findings of most American authors (Danowski, 1957 ; Cohen *et al.*, 1960), Fig. 2 shows that the episodes of ketosis were seasonal, being especially common in November and December and uncommon in May and June. We consider the seasonal incidence to be associated with respiratory infection, which was a common precipitating cause of ketosis.

Overall Mortality.—In the 160 episodes of ketosis 19 patients died, a mortality rate per episode of 12% (see Table and Fig. 1). We have included every death occurring in patients after admission to hospital with ketosis, even though it might have taken place many days afterwards. This is because in every case it seemed likely that delayed death would not have taken place had the patient not been in ketosis. Similarly, we have included all cases where ketosis and another serious illness occurred together, because it always seemed probable that ketosis had played some part in the fatal outcome. Ten deaths occurred within 24 hours and could be directly attributed to the ketosis; in nine patients death was delayed, and occurred between 2 and 15 days after admission. Since age has been one of the most important factors in determining the mode of death we have arbitrarily divided the fatal cases into three age-groups: 60 years and over, 20 to 59, and under 20.

Deaths in Patients Aged 60 and Over.—In the 30 episodes in this group 10 patients died, a mortality rate per episode of 33%. In seven patients death was delayed, and in five of these it was due to the effects of arterial thrombosis, which emerges as the commonest single cause of delayed death in the whole series. The thrombosed vessels were the abdominal aorta, the right common iliac, the right subclavian, the left internal carotid, and major branches of the splenic and renal arteries respectively. In every case the occlusion seemed to result from, rather than be the cause of, the ketosis, and the effects became apparent after the ketosis was controlled. The two other cases of delayed death were due to bronchopneumonia. Of the three elderly patients who died after admission to hospital, the history and symptoms of ketosis were atypical in two, and there was delay in diagnosis and treatment. In the third case the severity of the ketosis masked the presence of intestinal obstruction long enough to cause a fatal outcome.

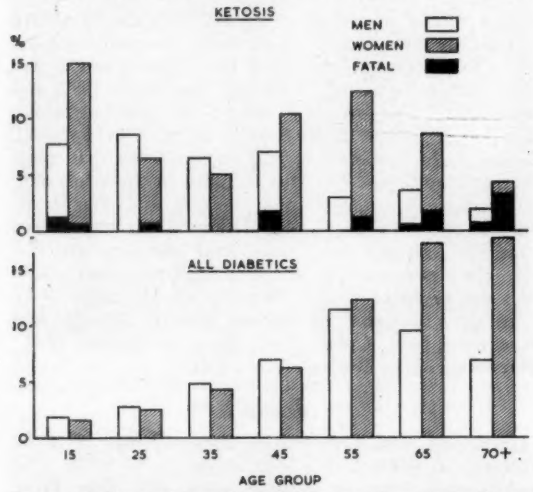

FIG. 1.—Incidence of severe ketosis in men and women in 10-year age-groups, compared with the prevalence of diabetes in the same age-groups in all patients attending the diabetic clinic.

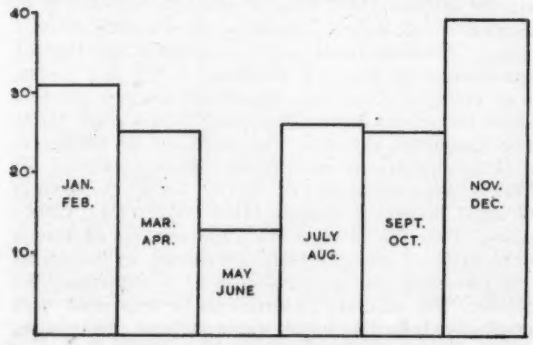

FIG. 2.—Seasonal incidence of severe ketosis.

Age Incidence of Ketosis for Both Sexes, with Number of Deaths

Age-group of Patients	Episodes in		Deaths	
	Males	Females	Males	Female
10–19	11	24	2	1
20–29	13	11	0	1
30–39	12	6	0	0
40–49	9	18	3	0
50–59	6	20	0	2
60–69	6	14	1	3
70–79	3	7	1	5
Total	60	100	7	12

Mean age of admission was 39·6 years.

Deaths in Patients Aged 20–59.—In the 95 episodes in this group, six patients died, a mortality rate per episode of 6.3%. Four of these were extremely ill from uncomplicated keto-acidosis and showed a number of unfavourable prognostic signs (Rabinowitch *et al.*, 1939). Thus compared with the survivors of the same age-group the mean duration of symptoms was twice as long (54 hours compared with 29 hours), the mean initial blood sugar twice as high (1,150 mg./100 ml. compared with 610 mg./100 ml.), and all presented in coma with systolic blood-pressure below 100 mm. Hg. Yet in two episodes death might have been avoided since the stomach had not been aspirated, and at necropsy there was inhaled vomit in the bronchi. Of the two other patients not in deep coma, one had acute pancreatitis and peritonitis and the other a myocardial infarction.

Deaths in Patients Aged 10–19.—In the 35 episodes in this group three patients died, a mortality rate per episode of 8.6%. All three cases were quite unexceptional in respect of the severity of the ketosis. The mode of death was so similar and so unlike the other fatal cases in the series that they merit more detailed description.

Case 1.—A 13-year-old girl not known to be diabetic had symptoms of a month's duration. She had vomited for two days and had air hunger for a few hours prior to admission, when she was drowsy but not unconscious. Her B.P. was 125/75, her blood sugar 530 mg./100 ml., and she had heavy glycosuria and ketonuria. Treatment consisted of 80 units of soluble insulin on admission and a further 40 units two hours later, together with an intravenous infusion of 1 litre of hypotonic saline lactate (Na 98 mEq/1, Cl 68 mEq/1, lactate 30 mEq/1. This was followed by 1 litre of potassium-containing solution (Na 56 mEq/1, K 24 mEq/1, Cl 44 mEq/1, lactate 24 mEq/1, HPO_4 12 mEq/1). Six hours later her clinical condition had improved, her blood sugar was 260 mg./100 ml., but she remained drowsy. She lost consciousness 10 hours after admission and died within a few minutes. At necropsy the only abnormal finding was cerebral oedema and bilateral tentorial pressure cones; histological examination of the brain showed patchy neuronal atrophy of anoxic type.

Case 2.—A 15-year-old boy not known to be diabetic was at work the day before he was admitted to hospital. He had severe symptoms of about a month's duration. He had slight air hunger, but consciousness was unimpaired. His B.P. was 135/80, and blood sugar 540 mg./100 ml. He

had heavy glycosuria and ketonuria. Treatment consisted of 80 units of soluble insulin and oral fluids. He suddenly became unconscious six hours after admission, his B.P. fell, and his breathing was for a short time periodic and then ceased. At this time the blood sugar was 288 mg./100 ml., Na 130 mEq/1, K 5.3 mEq/1, and HCO_3 12.1 mEq/1. In spite of an infusion of noradrenaline, a tracheotomy, and artificial respiration (I.P.P.) he died 30 hours later. At necropsy the macroscopic appearance of the brain was normal, and microscopical examination showed changes similar to those in Case 1, but more severe.

Case 3.—A well-built 16-year-old male diabetic, who had been on insulin for five years, started to vomit two days before admission. This had been precipitated by an infection of the upper respiratory tract. He was drowsy but rational; he had marked dehydration and air hunger. His B.P. was 120/70, blood sugar 546 mg./100 ml., HCO_3 9.5 mEq/1. He had heavy glycosuria and ketonuria. Treatment consisted of 250 units of soluble insulin and 4.5 litres of the hypotonic saline lactate, followed by 1.5 litres of the potassium-containing solution. During the first seven hours he passed nearly 2 litres of urine. He remained drowsy but otherwise seemed better. Eight hours after admission he suddenly became unconscious and was found to have large unequal pupils, hypotonic limbs, and bilateral extensor plantar responses. At this time his blood sugar was 200 mg./100 ml., Na 150 mEq/1, K 3.9 mEq/1, Cl 110 mEq/1, HCO_3 22 mEq/1, and urea 46 mg./100 ml. Soon after, a very marked increase in the urinary output was noted. This was found to be at the rate of 16 ml./min., with a specific gravity of 1003. The intense polyuria responded to "pitressin"; 5 mμ pressor units slowed the rate of urine flow immediately, but had to be repeated hourly. He did not regain consciousness; his respiration failed and the B.P. fell. He survived a further six days in a respirator, having continuous noradrenaline infusion. At necropsy the brain showed widespread necrosis of the hypothalamus and mid-brain, and we presume that the sudden unconsciousness followed by diabetes insipidus and progressive failure of respiration had resulted from this.

Discussion

Comparison of the percentage mortality figures from different centres for diabetic ketosis is difficult. This is in part because there is no agreement on the definition of severe ketosis, and partly because, as Rabinowitch *et al.* (1939) pointed out, no single feature expresses the severity of the individual case. There is therefore no certainty that any two series are composed of cases of comparable severity. Differences in the type of hospital, in the social structure of the population served, and in the level of general medical knowledge about diabetes outside the hospital all serve to influence the composition of any series. It is also well known that the prognosis of ketosis is grave over the age of 60, so that to some extent the mortality rate of any series is dependent on its age structure (Joslin *et al.*, 1959). These many variables make it difficult to assess to what extent differences in treatment influence the mortality rate. There seems little doubt, however, that the best results are obtained where a group skilled and experienced in the management of the condition undertake the treatment of every case (Harwood, 1951; Nabarro *et al.*, 1952).

From the sources of admission there is reason to believe that the present series is representative of the incidence of ketosis in the diabetic population. No special arrangements were made for treatment of the patients who were admitted under and treated by the physician of the day. Therapy was based on the principles suggested by Nabarro *et al.* (1952), and consisted of the immediate administration of large doses of soluble insulin together with intravenous infusion of hypotonic lactate-containing solutions. Potassium was given after about four hours and antibiotics were given from the start. We feel, therefore, that the mortality rate in this series is comparable with that of other large general hospitals in this country. Recent reports from elsewhere support this; thus Skillman *et al.* (1958) had 25 deaths in 172 episodes, and Greenaway and Read (1958) 11 deaths in 69. It is also of interest that in a series from this hospital collected in 1946–8 (Black and Malins, 1949) the mortality rate was no higher, in spite of the fact that at this time the importance of potassium depletion was not appreciated and the only fluid administered intravenously was isotonic saline.

The importance of arterial thrombosis as a cause of delayed death in elderly patients with ketosis has not been commented upon. It is hardly surprising, however, that haemoconcentration and circulatory failure should predispose to thrombosis in arteries already damaged by atheroma. The routine use of anticoagulants in cases such as this seems a justifiable prophylactic measure.

Of the 19 deaths in the series the three in adolescence followed a pattern not hitherto described. Structural cerebral damage has been found before in fatal diabetic coma (Dillon *et al.*, 1936); and Kety *et al.* (1948) have shown that a lowered cerebral oxygen uptake is a feature of fatal cases. In the cases described by these authors, however, the patients were unconscious on admission and had ketosis of the utmost severity. They are in contrast, therefore, to the above group, where loss of consciousness occurred suddenly when the response to treatment seemed adequate. Greenaway and Read (1958) report on seven cases, four of them fatal, where collapse characterized chiefly by a fall in blood-pressure occurred in similar circumstances. They thought the phenomenon to be unrelated to water or electrolyte repletion or adrenal insufficiency, but were unable to explain its cause. The clinical picture and necropsy findings in our patients suggest that sudden deterioration of this character is of central origin. In all three the sudden loss of consciousness was accompanied by signs of brain-stem disorder, while in one there was direct evidence of functional disturbance of the hypothalamus as evidenced by the unusual situation of coexisting diabetes mellitus and insipidus. The non-specific character of the pathological changes, together with the fact that the blood sugar and the blood electrolytes commonly measured were returning to normal at the time of the deterioration, suggests that other unrecognized metabolic factors were responsible.

Summary

The age and sex incidence in 160 episodes of severe diabetic ketosis is compared with the prevalence of diabetes at a hospital clinic. There is a large excess in the incidence of ketosis in adolescent girls.

The incidence of ketosis is common in November and December and rare in May and June.

Nineteen patients died—an overall mortality per episode of 12%. Ten deaths occurred within 24 hours of admission; in the remainder it was delayed and was the result of a superadded complication.

The death rate was high in patients over 60, and the commonest cause of death was thrombosis of a major artery.

Three deaths occurred in adolescence owing to progressive cerebral damage at a time the ketosis was

improving. In one there was massive destruction of the hypothalamus and mid-brain which gave rise to diabetes insipidus.

We thank Dr. W. T. Smith and Dr. R. Lannigan for the necropsy reports. This work was in part supported by a grant from the British Diabetic Association.

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THE RELIEF OF PAIN BY COOLING OF THE SKIN

BY

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In 1949 Dr. Janet Travell described the use of ethyl chloride spray in the treatment of acute wryneck. In 1951 Dr. W. A. Bain drew my attention to this work and suggested that this form of treatment might be of use in my department. Since that time I have used ethyl chloride in the treatment of so many painful conditions with such success that I should now be loath to run a busy casualty department without its help. In 1952 Travell described the use of the ethyl chloride spray in the treatment of painful muscle spasm giving a full bibliography, and pleaded for a wider trial of this simple therapeutic measure. In 1956 I reported locally my experiences with it (Ellis, 1956). Further advances have been made since then, and I should like to draw attention to the value of this treatment as revealed by nine years' experience of its use in this department, in the hope that others may try it.

Cooling of the skin by spraying with ethyl chloride has been used to treat all kinds of skeletal muscle pain, and also the pain of renal colic, of dysmenorrhoea, of migraine, and of causalgia; Taverner (1960) reports its use in post-herpetic neuralgia. The usual treatment of such conditions is by analgesics, from salicylates up to morphine and pethidine. Such analgesics succeed in dulling the pain to a greater or less extent, whereas the virtue of the spray treatment is that it abolishes the pain. That the pain may recur in some cases is no denigration of its efficacy, for many of these conditions require repeated doses of analgesics over a prolonged period to afford adequate comfort to the patient.

Types of Pain Relieved

Certain types of pain in which the spray has given dramatic relief are now described in more detail.

Lumbago

This term is used to cover a wide variety of types of low back pain. The acute, severe form presents a reasonably clear-cut clinical entity. The patient is seized with acute pain on getting out of bed in the morning or while bending and lifting a heavy weight. He presents a rigid back, and attempts to move increase the pain. Examination shows complete obliteration of the curve of the normal lumbar lordosis, often with scoliosis. When the patient lies prone on the examination couch the rigid straight back persists.

Treatment of this type of case is probably the most satisfactory use of the spray, for, in addition to relief of the pain, the deformity of the back can be seen to disappear. The lumbar region is vigorously sprayed for some 20 to 30 seconds. During the next few minutes the return of the normal lumbar curve can be seen to take place under the eyes of the surgeon, together with the disappearance of the scoliosis. When the patient turns to lie on his back he will admit that the acute pain has gone, but for some time there is a residual dull ache.

The after-treatment of such cases is usually rest in bed. With the abolition of pain and rigidity the patient can rest in comfort for whatever number of days is considered necessary. Some patients, however, have so much relief that they return to work on the same or the following day. Patients running their own small businesses are particularly grateful for the relief from the crippling pain, as it now allows them to continue at their work.

The more chronic types of low back pain often do not respond so dramatically. Travell has observed this also. But a large number of these cases do obtain such a considerable measure of relief that the spray is recommended as the first line of attack.

Acute Stiff Neck

I have often seen the dramatic sudden relief produced in this type of case, as reported by Travell. The patient who complains of a sudden "crick" in the neck on getting out of bed in the morning, and presents with acutely painful wryneck, is well known. Spray applied to the painful side of the neck brings dramatic relief.

Fibrositis

In the many cases of pain in muscles, in fascia, and around joints that can be lumped under this title, I regard the use of the spray as the first line of attack. Of the hundreds of patients who have attended this department in the last nine years, some have had complete relief after a single application of the spray. Others have had recurrences of pain and have required several sprays over some days. Two cases among my surgical colleagues are noteworthy. Each was afflicted with acute shoulder pain when called in to do emergency operations in the private wing. As a last resort, and without much hope of relief, they asked for the spray treatment. The spray gave them full, painless movement, and they were able to operate without disability.

Painful Scars and Causalgia

The use of spray in this type of pain produces relief where analgesics have failed to do so. In painful amputation stumps, spray treatment can be used either to replace or to complement percussion.

Renal Colic

The value of the spray treatment in relieving the agony of renal colic was, so far as we know, discovered in this department, in which we see some 30 to 40 cases a year. Renal colic is usually treated with large doses of morphine or pethidine, often with atropine or propantheline. Such treatment rarely brings immediate relief of pain. But the cold spray, applied from the renal angle down to the pubes, gives immediate relief from the colic. In many cases the general practitioner had given repeated doses of analgesics and finally sent the patient to me for admission. After being sprayed the patients said they were free from pain for the first time. I am now so sure that immediate relief follows spray treatment that recently, when a patient claimed no relief after three vigorous sprays and begged for an injection, I suspected that he was a pethidine addict. This suspicion was subsequently confirmed.

The cause of renal colic is usually a stone—and improved radiological techniques in our urology department now demonstrate the calculus in an ever-increasing number of cases. Colic may recur as the stone passes down the ureter, but these further episodes of colic will also respond to the spray. One patient visited me five times in four days for repetition of the spray, and after the fifth treatment the calculus was passed. It is my practice to refer patients to the next urological clinic for investigation and any necessary surgical treatment. In a large number of cases surgical intervention is now unnecessary, and the spray is used to treat any attacks of pain while the calculus is being passed *per vias naturales*.

Dysmenorrhoea

The use of a cold spray in this condition was evidently rediscovered in this department, for one case had previously been reported (Gardner, 1951). We see yearly some 25 to 30 young women who are brought in on a stretcher, "rolling in pain," sweating, and with a greenish pallor. A spray to the hypogastrium for 15 to 20 seconds gives instant relief. Within 10 minutes the patient walks out, with a normal colour and free from pain. Some of our own female staff have sought treatment, but many are too shy to come to a male doctor with this personal feminine complaint. Some of these young ladies treat themselves with the spray. One of my colleagues reported the incident of a nurse in the operating theatre who was almost disabled and fainting with the pain and was sent out to rest. She took a bottle of ethyl chloride out with her and returned five minutes later completely recovered, and continued her work for the rest of the morning without trouble.

The effect of the spray in renal colic and dysmenorrhoea is of great interest in consideration of the rationale of the treatment.

One further type of case of interest in this context is the fractured rib.

The Fractured Rib

We have learnt by experience that in the first few days after a fractured rib, although the spray does relieve the pain, the relief is so temporary that it is unwise to use it. While there is acute local tenderness at the site of the fracture, it is our practice to infiltrate carefully with procaine. After two to four injections the acute local tenderness disappears and a residual aching pain is left. At this stage the spray will produce relief lasting 24 hours and, later, for longer periods. The spray treatment is used for many types of post-traumatic pain of this nature with striking relief.

Rationale of Treatment

I am at one with Travell in thinking that the local anaesthetic action of freezing by cold plays no part whatever in the mechanism of relief. I agree that the spraying should not be prolonged so that freezing occurs. Travell goes into some detail on the importance of trigger points in the fascia or muscles in the mechanism and suggests that the spray acts on these points. Trigger points in fascia or muscles can hardly be incriminated in the production of the pain of renal colic or dysmenorrhoea. The theory is put forward that the spray acts by bombarding the central pain receptor areas with such a barrage of cold impulses that the pain impulses are swamped and obliterated. When the sensation of pain is obliterated the reflex arc is broken and the motor impulses causing muscle spasm stop. The muscle will relax. In renal colic the stone moves a little down the ureter. In spasmodic dysmenorrhoea the uterus relaxes, and a clot causing irritation can move away from the irritated area. In these types of case, when the barrage of cold impulses ceases there is no longer any source of irritation, and so no reflexes are set up and there is consequently no muscle spasm and no pain.

In the prolapsed-disk type of lumbago that I have described, similar relaxation of muscles occurs—they are seen to relax—and the prolapsed nucleus is no longer being squeezed out. With the absence of pressure this herniated mass ceases to press on the adjacent nerves and there is no cause for further pain when the cold wears off. Relaxation of skeletal muscles can be postulated to occur with disappearance of pain. In conditions like post-herpetic neuralgia and migraine a pain reflex mechanism has been set up which the barrage of cold impulses breaks. From the observed results in the treatment of fractured rib it is seen that the barrage of cold impulses obliterates the pain temporarily. But when the barrage ceases the cause of the pain is still present and unchanged and pain recurs. Later the cause of the pain in the rib is healing over, the spray breaks the pain reflex and relieves pain for much longer. The treatment, in fact, can be said to be vigorous counter-irritation.

Technique of Treatment

Although the rationale suggested is mere physiological speculation by a surgeon, producing a theory to account for the results, it indicates what is required in carrying out treatment by the spray. Since we wish the skin to remain sensitive to cold, we should not attempt to freeze it and render it anaesthetic. The pack of ethyl chloride put out by the makers for producing local anaesthesia ejects a very fine jet of liquid ethyl chloride on to the skin; this evaporates, extracting its latent heat of evaporation from the skin and freezes it. The use of this type of pack results in many failures, as would be expected from the hypothesis suggested.

What is required is a long nozzle of somewhat larger diameter which ejects the ethyl chloride in a fine spray,

the drops of which are already evaporating and are cold on reaching the skin. (Hedley No. 13 pack for general anaesthetics is the most suitable of those commercially available.) It follows that the nozzle should be held far enough away from the skin to allow the fluid to break up into cold droplets and not so far away as to produce only an attenuated blast of cold gas. With this pack 12 to 18 in. (30 to 45 cm.) is found to be a suitable distance. If these rather simple directions are borne in mind the rather elaborate technique recommended by Travell will be found to be unnecessary. The length of time the spray should be continued varies a little with the severity of the pain. The spray should not be so prolonged that skin-freezing occurs, and should be stopped at the earliest suggestion of freezing. To continue longer will produce no effect on anaesthetized skin, in addition to which a cold burn may result. Some of my colleagues find several repeated bouts of five seconds produce the required result. To obtain the mass barrage required, all the skin of the appropriate dermatome should be sprayed. In renal colic, lumbago, and dysmenorrhoea, to keep up the attack, the spray can be continued for 15 to 30 seconds, using about one-half to three-quarters of the bottle, before any sign of freezing appears.

Treatment by the spray is simple; the technique can be easily learnt and carried out by the general practitioner in the house or by co-operative lay persons. Many local general practitioners are using it with gratifying results. To give the ethyl chloride bottle to the patient for personal use in the home is not, however, without danger. Ethyl chloride is flammable, toxic, and anaesthetic. To get over these disadvantages, Dr. Travell and, later, Smith Kline and French Laboratories in Philadelphia experimented with inert liquids of low boiling-point so as to discover one with the same physical properties as ethyl chloride. Dr. Bain eventually produced a mixture of fluoromethanes for us, put up in a metal canister similar to that used in household aerosols. If this spray pack ("skefron") is held a little farther away from the skin than ethyl chloride the cold effect on the skin is almost identical and the clinical results are comparable. We have given these canisters to a number of patients experiencing various kinds of pain, for them to take away for home use. One patient with moderately severe low-back pain was relieved by the skefron spray used in this department and asked for help to continue in his newly started business as a painter and decorator. He was given a canister to take home. At the end of a week he returned asking for a further supply. He told us that, although his pain had recurred at intervals, the skefron spray had relieved it so much that he did not have to give up any of his work.

Summary

Some papers recommending the use of ethyl chloride spray in the treatment of acute pain associated with muscle spasm are reviewed.

Nine years' experience in the casualty department of the General Infirmary at Leeds with the ethyl chloride spray for the treatment of acute pain in many conditions is described. These painful conditions include lumbago, acute wryneck, fibrositis, renal colic, dysmenorrhoea, and fractured rib.

A theory is put forward to account for the many striking successes achieved and also to account for the failure in some cases. The technical points necessary for success are discussed. A new fluoromethane product, skefron, which is non-toxic and non-flammable and gives the same results as ethyl chloride, is described.

I am indebted to Dr. W. A. Bain for his long-continued interest in this treatment. The new product, skefron, was evolved at his suggestion. To Smith Kline and French Laboratories, Philadelphia, I am indebted for liberal supplies of fluoromethane mixtures for clinical trial.

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OSTEOSCLEROTIC BONE CHANGES IN PRIMARY HYPERPARATHYROIDISM WITH RENAL FAILURE

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It is well recognized that primary hyperparathyroidism may cause a serious form of renal disease (Albright *et al.*, 1934; Richardson, 1953). It is also a well-established fact that chronic renal insufficiency may result in secondary hyperplasia of the parathyroid glands (Albright *et al.*, 1937; Castleman and Mallory, 1937; Shelling and Remsen, 1935). Bone changes are sometimes detectable radiologically in these latter patients, and they then resemble closely the changes in primary hyperparathyroidism (Dent and Hodson, 1954; Stanbury, 1957). Osteoclerosis may develop in cases of renal failure, although it is an uncommon radiological finding (Crawford *et al.*, 1954; Karani, 1955; Wolf and Denko, 1958), and the demonstration of osteosclerosis in a patient with hyperparathyroidism has been taken to show that hyperparathyroidism is secondary (Brookfield *et al.*, 1955). However, the renal damage resulting from primary hyperparathyroidism could presumably produce osteosclerosis similar to that seen complicating primary renal disease. A case was reported by Beveridge *et al.* (1959) of a patient with a parathyroid adenoma in whom renal failure was present and radiological examination showed presence of marked osteosclerosis.

We wish to report the case of a patient who we believe had primary hyperparathyroidism, osteosclerotic bone changes, and renal failure. A further unusual feature was that of calcification in a haemorrhagic parathyroid cyst.

Case History

A spinster aged 63 was first seen by one of us (R. G. P.) at the request of Mr. M. P. McCormack, to whom the patient had been referred with a fracture of the right radius. The first symptom possibly attributable to her bone disease had occurred in 1955, when she attended another hospital

on account of pain in her right knee. Clinically she was thought to have an effusion, and was treated for osteo-arthritis without any improvement. By 1958 she had developed pain in both knees, the right shoulder, and the right forearm; she also complained of an "occasional" swelling in the forearm.

In July, 1959, while using a hammer, she suddenly developed pain at a site corresponding to the swelling, and radiographs revealed a fracture through a "cystic" area in the radius. At no time had there been any urinary symptoms and there was no preceding history of renal disease.

On admission here she was found to have a well-marked kyphosis together with a prominent sternum. In addition, on the right side of the neck there was a hard round irregular mass which moved on swallowing.

Biochemical findings gave the following results (the details are shown in Fig. 5). Plasma calcium, 10.5 to 10.7 mg./100 ml.; plasma phosphate, 3.1 to 3.5 mg./100 ml.; total proteins, 6.3 to 6.7 g./100 ml.; blood non-protein nitrogen was raised 62 to 81 mg./100 ml. Three consecutive 24-hour estimations of urinary creatinine and calcium gave calcium/creatinine ratios of 0.27, 0.24, and 0.23. Endogenous creatinine clearance was estimated at 19% average normal clearance. On two occasions a urine concentration test gave a maximum concentration of 1009.

The first radiological film, that of her chest, was taken in 1950; this showed no abnormality in either the ribs or the lung fields. By 1958 well-marked skeletal changes were present, and films of the neck taken at this time showed a calcified opacity in the right sternoclavicular region (Fig. 1); this opacity had produced both tracheal and oesophageal compression.

In 1959, radiographs of the tibiae, fibulae, and forearm bones showed widespread rarefaction, while the hands also showed subperiosteal absorption and several "cystic" areas (Fig. 2). In addition "cystic" changes were present in both tibiae, and the right radius showed an expanding "cyst" at the site of the previous fracture, which was accompanied by organizing periosteal new bone. *X*-ray examination of the skull revealed an alteration in bone texture of the vault.

Intravenous urography showed that the kidneys were small and that the contrast medium was poorly concentrated. No nephrocalcinosis was visible. The lumbar vertebrae were seen to have the typical osteosclerotic appearances known as "rugger jersey" vertebrae (Fig. 3).

FIG. 1.—Tomograph showing calcified opacity in right sterno-clavicular region.

FIG. 3.—Radiograph of lumbar spine, showing "rugger jersey" appearances.

FIG. 2.—Radiograph of the hands, showing rarefaction, subperiosteal erosions, and cystic areas.

FIG. 4.—Specimen removed at operation.

The biochemical findings were considered to establish a diagnosis of primary hyperparathyroidism. This diagnosis was supported further by a plasma calcium estimation of 11.1 mg./100 ml., with the plasma phosphate 2.8 mg./100 ml. immediately prior to the operation.

On February 1, 1960, the thyroid gland was exposed through a collar incision (R. G. P.). An encapsulated and calcified swelling was at once obvious, occupying most of the lower and posterior part of the right thyroid lobe, which from its position could well have been parathyroid in origin. Macroscopically, however, it did not resemble any lesion of these glands. In addition the relatively large size of the swelling tended to cast doubt on its being a true parathyroid tumour. A second and much smaller swelling (1 by 0.5 cm.) was seen in the upper and posterior aspect of the right lobe and was thought possibly to be parathyroid, but immediate section revealed normal thyroid structure.

A complete right hemithyroidectomy was performed and a thorough search made in the exposed tissues for positive evidence of parathyroid adenoma, but without success. The question then arose whether the mediastinum should be explored, but in view of the patient's poor general condition this was not seriously considered.

The specimen removed (Fig. 4) was the right lobe of the thyroid, to which was firmly attached an oval encapsulated swelling (6 by 5 by 4 cm.). The cut surface of this swelling showed it to be haematoma with fibrous and calcified walls, with at the lower end soft yellow tissue which proved on section to be parathyroid adenoma. Section of the calcified wall, including the haematoma, showed small scattered islands of parathyroid tissue both within the main capsule and in the fibrous capsule. The encapsulated swelling showed no thyroid tissue. The conclusion was that this parathyroid tumour, which contained a large number of thin-walled blood spaces, may have bled many years ago to form a haematoma, the walls of which had subsequently become fibrotic and calcified.

After operation, the plasma calcium levels fell (Fig. 5), remaining low despite calciferol, and rising again only on treatment with high doses of calciferol and calcium carbonate powder. These, however, were stopped on March 25 in view of the rising blood non-protein nitrogen, which was considered to reflect possible further renal damage as a result of the high calcium intake; during this period the urine calcium/creatinine ratios were of the order of 0.35 to 0.66. By the time of discharge (April 20) from hospital, further radiographs had shown that reossification was occurring throughout the skeleton, and the cystic changes were regressing. However, little change was apparent in the "rugger jersey" appearance of the spine.

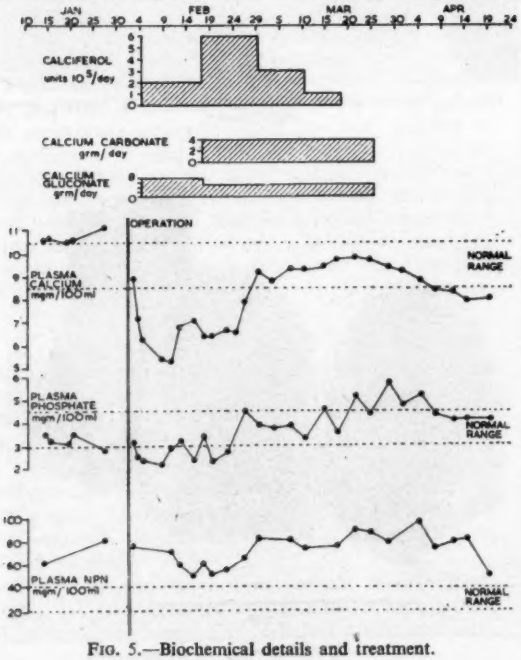

FIG. 5.—Biochemical details and treatment.

Discussion

The findings of an encapsulated tumour with the histological appearances of an adenoma, together with the biochemical findings enumerated above, establish the present case as one of primary hyperparathyroidism. Also the raised plasma non-protein nitrogen and the considerable reduction in endogenous creatinine clearance show that renal damage coexisted. In the absence of any preceding history of renal disease these changes presumably arose as a result of the hyperparathyroidism. Such a complication is well recognized and is usually due to nephrocalcinosis.

In addition, *x*-ray examination of the patient's thoracic and lumbar vertebrae showed the changes known as the "rugger jersey" spine. Essentially, this appearance is due to a horizontal layer of less dense bone being sandwiched between an upper and a lower layer of osteosclerotic bone, the latter being due to excessive osteoblastic deposition at vertebral margins.

It has been stated by Brookfield *et al.* (1955) that "the finding of osteosclerosis in hyperparathyroidism would at least exclude the hyperparathyroidism as a primary disease." In view of the findings described above, it would appear that this contention is incorrect and that no significance should be attached to these appearances in determining the primary or secondary nature of the parathyroid activity. What does seem likely is that these changes are indicative of renal damage irrespective of whether this is the cause or the result of the hyperparathyroidism. This view is supported by the cases of Crawford *et al.* (1954) and of Karani (1955), in which renal failure had given rise to secondary hyperparathyroidism, both their cases having "rugger jersey" vertebrae. Beveridge *et al.* (1959) have also described a case which, like our own, had primary hyperparathyroidism, secondary renal failure, and a "rugger jersey" pattern.

It is known that areas of osteosclerosis may develop in the skeleton of patients with long-standing renal failure without manifest evidence of hyperparathyroidism. Crawford *et al.* (1954) described such cases with increased uniform density of spine, skull, pelvis, and long bones. It does appear, therefore, that a relationship exists between renal failure and new bone formation, but the distribution pattern and severity of the osteosclerosis are variable. Precisely what the relationship is remains obscure, although the fact that the blood-forming bones are those affected and that such patients are anaemic has given rise to the suggestion that the anaemia may be a factor of importance (Karani, 1955). In this connexion it is of interest that our patient had no marked anaemia.

Another unusual feature in this case was the large size of the parathyroid tumour. Pre-operatively it was thought, as a result of clinical and radiological investigation, to be due to a goitre, and the presence of well-marked calcification in the neck was thought to be due to calcification in a thyroid cyst. Subsequently a review of the literature has shown that, although several cases of parathyroid adenomata simulating goitres have been described, radiologically detectable calcification is

rare and we have been able to discover only one case (Bogdonoff *et al.*, 1956). It is therefore not surprising that evidence of histological calcification is also uncommon.

Summary

A patient with primary hyperparathyroidism and renal damage had the radiological picture of "rugger jersey" spine due to zones of osteosclerosis. This appearance does not, as has been stated, show that the hyperparathyroidism is secondary to renal damage, but merely that renal damage coexists.

We thank Drs. G. K. McGowan and F. G. M. Ross for advice in the preparation of this paper; Dr. J. E. Cates, who was responsible for the post-operative care; and Dr. O. C. Lloyd for permission to use his histological report.

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Medical Memoranda

Lateral Cervical and Preauricular Sinuses: Their Transmission as Dominant Characters

Lateral cervical sinus or fistula is not an unfamiliar condition to the paediatric surgeon. Gross (1953) reports 148 cases from the records of the Boston Children's Hospital, 25 of them bilateral. It is also known as "branchial sinus or fistula," a designation which appears in most of the standard surgical textbooks.

The name "fistula" is used here when referring to a "complete" lesion which communicates with both the skin and the pharynx, the name "sinus" when referring to an incomplete lesion that communicates only with one of them (nearly always the skin) (Aird, 1949).

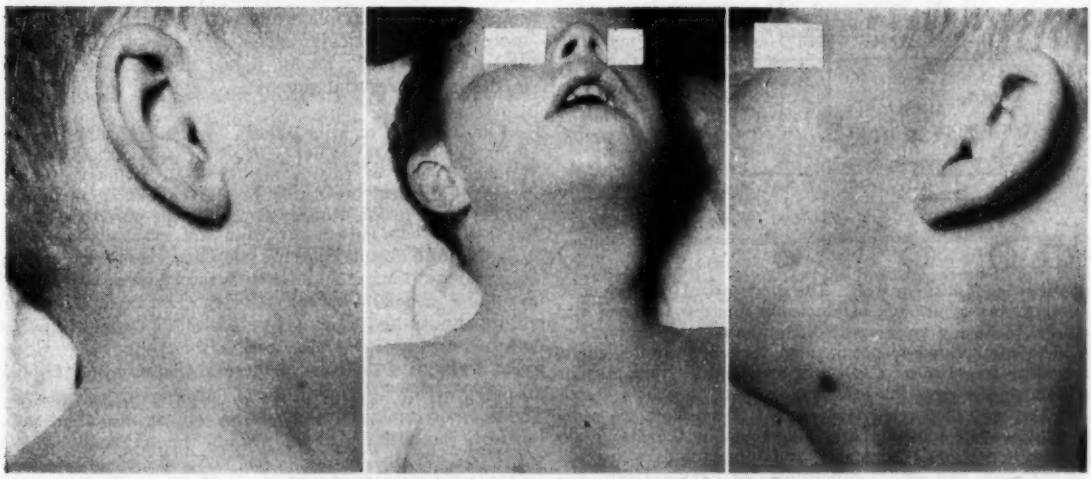
Preauricular sinus is also not rare in a children's hospital. Gross (1943) reports 44 cases, of which 12 were bilateral.

Embryology

Lateral Cervical Sinus.—In the first two or three weeks of embryonic life, four (or possibly five) grooves develop in either side of the neck, running obliquely downward, forward, and somewhat medially, which are called the branchial clefts. They are matched internally by outpocketings of the foregut which are the branchial pouches. They delimit in between them the branchial arches, which later will give rise to the neck and lower part of the face. By the fifth week an overgrowth of the second branchial arch will extend down in front of the arches caudal to it, forming the precervical sinus (the cephalic portion of which is the second branchial cleft). The lateral cervical fistula is derived from the second branchial pouch, and the precervical sinus. The lateral cervical sinus, opening in the skin, derives only from the latter. Confirmation of that origin is given by the usual findings at operation; (*a*) that the fistulous tract runs in between the internal and external carotid arteries, the former from the second branchial arch and the latter from the third; (*b*) that the pharyngeal opening, when it exists, lies in the tonsillar fossa, which corresponds to the internal end of the second pouch.

Preauricular Sinus.—The different parts of the ear arise from six small nodules, first described by His (1885), which develop around the dorsal extremity of the first branchial cleft. The three nodules from the first arch would give the tragus and helix, and the three nodules from the second arch the antitragus and antihelix.

Though no agreement exists about the origin of preauricular sinuses, according to Aird (1949) the least objectionable hypothesis regards them as the result of the inclusion of part of the angle between the base of the first tubercle and the adjacent skin. The direction and length of the sinus would be due to the growth of the mandibular process with downward and forward stretching of the overlying skin, while the bottom of each groove would remain fixed.



Photographs showing lateral cervical and preauricular sinuses.

CLINICAL AND PATHOLOGICAL DATA

Mucoid discharge is commonly a presenting symptom in lateral cervical sinus. A small orifice is usually present since birth along the lower third of the anterior border of the sternomastoid. Especially in the cases of recurrent infection, which are frequent, that orifice develops a crescentic upper border with scarring and puckering above it, and moves when swallowing. The sinuses are lined either with ciliated or non-ciliated columnar epithelium or by stratified squamous epithelium, with a wall rich in lymphoid tissue. Apart from the cases described by Kindar (1954) no others have apparently been reported as containing muscle in their wall.

The most common place for "ear pits" is in the preauricular position. They are narrow blind sinuses, usually only a few millimetres deep, rarely becoming infected. They are lined by squamous epithelium only.

TREATMENT OF LATERAL CERVICAL SINUSES

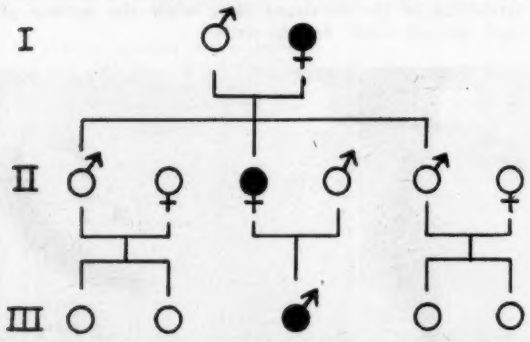
Routine excision always when no inflammatory signs are present. In preauricular sinus, if uncomplicated, routine excision is not necessary. In both conditions, if an abscess has formed it must be treated as such, and incision and drainage performed prior to removal of the lesion.

CASE REPORT

The patient was first seen at the Royal Liverpool Children's Hospital on May 23, 1958, when 5 years old. Since birth small sinuses had been present on both sides of the neck. The sinus on the left side had been discharging intermittently for the previous three years, and an underlying swelling had occasionally been noticed.

On examination he was found to have a typical right branchial sinus at the level of the cricoid. The left sinus opening was at the same level, but a very large abscess discharging pus was present underneath. It was noticed that the child also had bilateral preauricular sinuses (see photographs).

The left branchial sinus required incision and drainage twice, but it was impossible to eradicate the infection completely, and it was decided to excise the bilateral sinuses under antibiotic cover. This was done with oxytetracycline, to which the haemolytic streptococcus grown pre-operatively was found to be sensitive. The excision was performed on September 17, 1958, and he made an uneventful recovery.



both wounds healing well. The diagnosis of the branchial sinuses was confirmed histologically, but the left one was found to have a large cystic dilatation at its distal portion.

The mother, who accompanied the child to the clinic, was also found to have bilateral branchial and preauricular sinuses. She gave the information that the child's grandmother, who died relatively young, suffered from the same condition. None of the other members of the family on the maternal side (two uncles, and four cousins whose sex is unknown) had similar complaints (see Family Tree).

The patient's mother died recently at the age of 31. A diagnosis of chronic nephritis was made. Unfortunately, no I.V.P. was ever done and permission for a post-mortem examination was refused. Though the child did not have symptoms, the history and his rather peculiar facies (vaguely reminiscent of the facies in renal agenesis) prompted us to do an I.V.P., and this in fact confirmed our suspicions. It showed a very small hypoplastic right kidney and some dilatation of the pelvis of the left kidney, with caliceal abnormality, the superior calices seeming to be absent.

COMMENT

It is well known that preauricular sinus is inherited as an incomplete dominant of variable manifestation and without sex difference. Heusinger (1864) was the first to note the familial occurrence of the complaint. According to Aird (1949), the frequency of such a lesion in a small community including several affected families can be as high as 5%. Still quoting Aird, Sir Arthur Keith in 1909 illustrated the occurrence of preauricular sinus with other congenital abnormalities, such as cleft-palate, spina bifida, and imperforate anus.

In our patient definite congenital renal anomalies are present (and most probably were in his mother).

Last but not least, because it is in fact the main reason for this case report, there is the existence of bilateral lateral cervical sinuses in the child, his mother, and grandmother, strongly supporting the idea that they can be transmitted through a dominant Mendelian factor. So far as we have been able to investigate, only one case has yet been described in which a male patient, his father, and his grandfather all suffered from a right lateral cervical sinus (Kinder, 1954) though with no other associated anomalies.

Another point of interest is that, in our case as in that of Kinder, a cystic dilatation was present in the course of the fistula, which is most unusual and normally is considered to be the result of secondary dilatation of the tract after obstruction and infection. Because in our patient such a cyst arose only on the infected side, we think that Kinder's suggestion that in his patients the cyst formation was not due to chance complication but to a Mendelian dominant factor can be rejected.

Also of note is that the lateral cervical sinus appeared bilaterally in all of our three cases, and that in Kinder's three cases it was apparently on the same side (right). This has been observed to happen with preauricular sinuses, where in unilateral cases they tend to appear more on one particular side (right or left) (Edmonds and Keeler, 1940). So far it had not been recognized in the lateral cervical sinus.

I am indebted to Miss Isabella Forshall for allowing me to publish this case; to Dr. G. W. Roberts, Flintshire County Council Officer of Health, and Miss M. Williams, health visitor, for their invaluable help in obtaining a family history; and to Mr. Rodney Green for the photographs.

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Agranulocytosis after Imipramine and Meprobamate

We have lately observed the fatal outcome of agranulocytosis in a patient after treatment with imipramine ("tofranil") and meprobamate ("equanil") for involutional depression. As both drugs have the reputation of low toxicity and a low incidence of fatality, this case is of interest.

CASE REPORT

A multipara aged 56 was admitted to hospital on April 9 with a history of depression of varying severity and of at least four months' duration. She had been treated for 41 days with meprobamate in 400-mg. doses t.d.s. and imipramine, 25 mg. t.d.s., the dosage of the latter being increased to 50 mg. t.d.s. 10 days before her admission. She was drowsy and restless and looked critically ill. She complained of sore throat and dysphagia lasting three to four days, was running a temperature of 100.4° F. (38° C.), and had large necrotic ulcerations of the palates and fauces, with bilateral tenderness of the cervical glands.

Investigations.—Urine: albumin +++; deposit nil. Hb, 72% (10.7 g./100 ml.); R.B.C., 4,000,000/c.mm. (reticulocytes, 0.2%); platelets, 120,000/c.mm. Total white cells, 2,100/c.mm. (neutrophils 2%, lymphocytes 83%, monocytes 15%). Liver-function tests: direct bilirubin, 1.2 mg./100 ml.; total bilirubin, 2.1 mg./100 ml.; alkaline phosphatase, thymol turbidity, and flocculation, normal values. Swabs from throat grew coliforms in a mixed culture.

The clinical picture was one of agranulocytosis. Antibiotics, blood transfusion with packed cells, vitamin B_{12}, and cortisone were given. However, the white-cell count fell to 1,400/c.mm. and the neutrophils to 1%. Terminal bronchopneumonia with right ventricular failure ensued, and she died on her sixth day in hospital.

The histology showed central necrosis with pigment deposits in degenerate cells of the liver; oedema, haemorrhages, and areas of necrosis in the lungs; toxic nephrosis; necrosis of the mucosa covered by heavy growth of fungi in the oesophagus; hypoplasia and fatty infiltration of the bone-marrow, the granulocytes being mainly affected.

COMMENT

Attention has been drawn to the toxic side-effects and hazards of meprobamate (*British Medical Journal*, 1958) and its various idiosyncratic manifestations (Charkes, 1958). Only one fatal case of blood dyscrasia can be traced in the literature (Meyer *et al.*, 1957).

Imipramine can also give rise to numerous untoward side-effects (Fullerton and Boardman, 1959; Segal and Howarth, 1960), and in overdoses to epileptiform convulsions (Brooke and Weatherly, 1959; Levene and Lascelles, 1959) leading to death (Manners, 1960). Leyberg and Denmark (1959) report on a man of 60 who, after four months on imipramine, developed transient leucopenia with stomatitis. Four cases of agranulocytosis have so far been published. The first one (Rothenberg and Hall, 1960), that of a 64-year-old man who manifested the first symptoms after 38 days of taking the drug, recovered. The second reported case ended fatally (Morgan-Hughes and Heald, 1960). It concerned a 72-year-old woman who had been ingesting the drug for 45 days with *Rauwolfia canescens* and amylobarbitone. In the third and fourth reported cases the patients recovered. The former (Bird, 1960), a woman of 44, fell ill after taking the drug for eight weeks, along with salicylates and steroids for her rheumatoid arthritis. The latter (Cohen, 1960), a woman of 70, had been treated for her depressive illness with a daily imipramine dosage of 225 mg. and occasional small infrequent doses of quinalbarbitone for eight weeks, with some interruption, before the clinical picture of a mild agranulocytosis developed. Our patient took the drugs, as mentioned, for 41 days.

It is difficult to say whether meprobamate or imipramine was the culprit, but it is more likely to be imipramine, as it was the common drug used in the cases mentioned above with similar symptomatology and identical aetiology.

Segal and Howarth (1960) raised the question of serious effects of synergic action of other such drugs as chloral and aspirin in large doses on the one hand and the monoamine oxidase inhibitor type of antidepressant drugs in normal doses on the other.

It is striking that the ill-effect of imipramine alone or in combination, in almost all the cases cited above, occurred in elderly persons. Furthermore, the onset of agranulocytosis was manifest in five to eight weeks after the first ingestion of the drug. In the case of severe but reversible leucopenia (Leyberg and Denmark, 1959) the clinical symptoms began even four months after the drug was first given. One would expect an allergic reaction to a drug at the beginning of its ingestion rather than after five to eight weeks. The pathology of our case and that of others indicates toxic aetiology.

Conclusions.—Even if the patient has no side-effects during the first two or three weeks of administration, all is not necessarily well. It would therefore be advisable to carry out white blood counts, at least after four to five weeks of taking the drug and at intervals of two to three weeks thereafter, especially in the elderly, as a low white blood count—say around and below 3,000/c.mm.—may give warning of an impending catastrophe. The administration of imipramine, and particularly its combination with other drugs, needs caution.

We are indebted to Dr. W. Doran, pathologist, for his report on the pathological histology of the case.

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The effect that variations in pressure, temperature, and humidity have on radiation dosimeters—whose unit of measurement, the roentgen, is defined in relation to standard air conditions—is discussed in a recent publication of the National Physical Laboratory, *The Effect of Variations in the Ambient Air on the Calibration and Use of Ionization Dosemeters*. Tables of correction factors are given which, particularly in relation to humidity variations, are a valuable aid in precision dosimetry. (By G. P. Barnard, G. H. Aston, and A. R. S. Marsh. H.M.S.O., price 2s. 6d., by post 2s. 10d.)

Reviews

HEART SURGERY

Modern Trends in Cardiac Surgery. Edited by H. R. S. Harley, M.S., F.R.C.S. (Pp. 282+xiii+12; illustrated. 70s.) London, Toronto, Sydney, Wellington, Durban: Butterworths. 1960.

From this book the reader can gain a very good idea of the current practice of heart surgery in this country, and indeed, the list of the authorities who have contributed to this book is a testimony to the quality and accuracy of the information that is provided. It is essentially a practical outline of what is being done routinely in the cardiac units of Great Britain and is a tribute to the enterprise of young surgeons and their colleagues who have made this branch of surgery possible.

The opening chapter by Richardson is a concise and accurate account of the history of cardiac surgery, and this is followed by the editor's section on haemodynamics. Harley discusses clearly the effects of circulatory adjustments to increased resistances and shunts with special reference to the factors concerned in obstructed pulmonary venous return and pulmonary hypertension. After these introductory sections individual abnormalities are discussed by surgeons who have had special experience. It would be invidious to select any one chapter as being more outstanding than its neighbours, but the accounts of coarctation of the aorta and Fallot's tetralogy are unusually good and clear. Special techniques are discussed adequately by acknowledged experts in each section—hypothermia by Ross and Sellick, extracorporeal circulation by Melrose, and profound hypothermia by Drew. Waterston deals with the special problems encountered in the first year of life, and Barrett completes the book with a philosophical essay on the future of cardiac surgery.

Minor criticisms are inevitable: little is said about transventricular mitral valvotomy, and the illustrations and diagrams are not all oriented in the same plane. But in general the contributors and their editor are to be congratulated on the high standard achieved. One contributor, Paul Chin, to whom the book is dedicated, did not live to see its completion. The impression of vitality and energy that underlies the practice of cardiac surgery pervades the whole work. Anyone of any age or any specialty in medicine will benefit from the information collected into a short space from many sources.

T. HOLMES SELLORS.

AN OBSTETRIC CLASSIC

Antenatal and Postnatal Care. By F. J. Browne, M.D. (Aberd.), D.Sc., F.R.C.S.(Edin.), F.R.C.O.G., and J. C. McClure Browne, B.Sc., M.B., B.S., F.R.C.S.(Edin.), F.R.C.O.G. Ninth edition. (Pp. 435+viii; illustrated. 45s.) London: J. and A. Churchill Ltd. 1960.

A new edition of this famous book is an important event in the field of obstetric literature. Father and son again co-operate to preserve the standard and familiar outlook of a work which has been a best-seller for 25 years. In doing so they have reduced its size by approximately 200 pages. This remarkable achievement is brought about in part by a slight increase in page size but mainly by pruning of the text.

Chapters on heart disease and on obstetric radiology are contributed by Professor John McMichael and by Professor Chassar Moir respectively. The late Dr. Grantly Dick-Read's chapter is now superseded by a shorter and more balanced account of the physical and mental preparation for childbirth. The present rapid shift of peoples is catered for by sections on air travel and on intestinal parasites. There is also a short account of oliguria and anuria complicating abruptio placentae. But basically the book remains the same and presents an easy, conservative, and traditional account of the management of pregnancy and its complications, its even tenor unruffled by many of the new, exciting, and sometimes disconcerting ideas and observations which abound to-day. It is these staid qualities which will make this edition, as they did its predecessors, popular with postgraduate students throughout the world. These men and women, after all, have to learn what will satisfy examiners who, they imagine, will look askance at what savours of advanced views. Since their potential readers have such diverse backgrounds and working conditions, the authors are no doubt wise to maintain their cautious approach.

T. N. A. JEFFCOATE.

CRASH INJURIES

Crash Injuries. The Integrated Medical Aspects of Automobile Injuries and Deaths. By Jacob Kulowski, M.D., F.A.C.S., F.I.C.S. (Pp. 1,080+xiii; illustrated. £13.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

This work of over 1,000 pages has brought together in one volume a mass of new and valuable information. Undoubtedly it is the most comprehensive study yet published on the many aspects of road traffic accidents.

Much of the data is from the author's personal and considerable investigations as a practising surgeon. He also presents valuable summaries of the findings of all major American studies, such as the extensive surveys of the Cornell Group and the heroic experiments of Colonel J. P. Stapp on deceleration from high velocities, the work of Dye on simulated crashes, and the research studies of the Institute of Traffic and Transportation Engineering in Los Angeles. All give basic data of the forces assaulting car occupants and the tolerance of the human body to such violence.

The subjects presented in the first two sections of the book will be unfamiliar to the majority of readers—for example, "biomechanics," the study of the human body as a mechanical system, and "pathomechanics," relating crash impact on various anatomical structures to vehicle design. These studies contain data essential to a clearer understanding of the forces leading to injury. From such basic knowledge, doctors working with engineers and others can take further action that must eventually lead to safer "packaging" of car occupants.

A large part of the book is devoted to treatment from the stage of first-aid to final rehabilitation. Injuries to each anatomical system are considered in separate chapters, as is the systemic response to major trauma. There follows a brief account of the medical and psychological factors predisposing to accidents, and a final chapter on the present and future challenge road traffic accidents present to modern medicine.

The book is beautifully produced, very clearly printed, and has over 600 excellent and often vivid line drawings and photographs that help considerably in understanding the text. The author's style of writing (a preference for circumlocution) will annoy most readers on this side of the Atlantic; it often confused this reviewer and made a few paragraphs meaningless. More thorough editing could eliminate this and some

unnecessary repetition. The work would also be much improved by an index, for its value as a book of reference is considerable. Judging the work as a whole, these are very minor points of criticism. The author has achieved his main objective, the production of a truly comprehensive, new, and authoritative study of the most important medico-social subject of modern times.

WILLIAM GISSANE.

VIRUS PATHOGENICITY

Virus Virulence and Pathogenicity. In Honour of Professor J. Mulder. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. Ciba Foundation Study Group No. 4. (Pp. 114+viii; illustrated. 12s. 6d.) London: J. and A. Churchill, Ltd. 1960.

The Ciba Foundation's one-day study groups are arranged round the work of an eminent scientist on the Foundation's scientific advisory panel. This booklet records the papers and discussions on virus virulence and pathogenicity held in honour of Professor J. Mulder, who has contributed much to the study of influenza. As pointed out by Sir Macfarlane Burnet, no complete picture of virulence could be expected from this meeting, but the papers and subsequent arguments revealed new viewpoints which should indicate lines for future work.

The most controversial topic was the apparent variation in virulence in different pandemics of influenza. In a provocative and well-reasoned paper, Dr. Ed. Kilburne argued that this could be due entirely to variation in the susceptible human populations and their bacterial flora, rather than to changes in the virulence of the virus strains themselves. Subsequent discussion showed that this view was not generally accepted, but there are clearly insufficient data to decide. Other papers and discussions were concerned with virulence at the cellular level, infections in human volunteers, the lessons to be learned from myxomatosis, and, of course, the problem of virulence in live virus vaccines.

One is impressed by the difficulty of discussing virulence and pathogenicity without more precise definition. Professor Stuart Harris, who bravely tackled this problem in the first paper, shows how various are the meanings and measurements of these attributes of micro-organisms, and Dr. H. R. Morgan even pointed out that one virus may be virulent because it kills cells, and another because it stimulates cells to grow. Perhaps it would be best if the words "virulence" and "pathogenicity" were abolished altogether, provided this did not hinder research or discussion on the subject matter of this stimulating booklet.

MICHAEL STOKER.

PERIODIC MENTAL DISORDERS

Periodizität in der Psychopathologie (Neuro- und Allgemeinpathologie). By Dr. E. Menninger-Lerchenthal. (Pp. 310+vii. 94s.) Vienna, Bonn, Berne: Wilhelm Maudrich Verlag. 1960.

Periodicity is at the same time one of the most obvious and most elusive features of many mental disorders. It is often difficult to be sure whether assumptions concerning periodicity stem from clinical observations or from folklore. Recently there has been a revival of interest in periodic mental disorders which seem to lend themselves to clinical experiments.

The author, who is associate professor of psychiatry and neurology in the University of Vienna, defines periodicity as the tendency to phasic recurrence. Regularity in the length of the phases and of the intervals is not regarded as essential. He is chiefly interested in the abnormal physiological processes accompanying periodic mental disorders. He sets out to test the hypothesis advanced by many writers that periodicity in mental disorders is due to some kind of dysfunction of the pituitary-hypothalamic system. He has assiduously collected a mass of observations and speculations from the literature from the beginning of this century up to the present time, mostly, though not exclusively, German. He surveys the knowledge of the periodicity of physiological functions in general with special consideration of the instincts and of sleep. He regards certain types of periodicity as established—that is, the 48-hour rhythm occurring in various mental disorders, phases lasting three days and recurring in intervals of four days, four-weekly periodicity, seasonal recurrence, etc. He believes that drugs acting on the hypothalamus can sometimes influence the course of periodic psychoses, and that the effect of electro-convulsive therapy is due to its impact on the function of the hypothalamus. There is a brief chapter on periodic phases in the creative productivity of men of genius. The author deserves gratitude for having undertaken the arduous task of collecting material for the use of future research workers.

The book has an extensive bibliography, but, unfortunately, no index, which is all the more regrettable as the main value of this work lies in its usefulness as a reference book.

E. STENGEL.

MITRA OPERATIONS

Mitra Operation for Cancer of the Cervix: Extraperitoneal Pelvic Lymphadenectomy and Radical Vaginal Hysterectomy. By Subodh Mitra, M.B.(Cal.), Dr.med.(Berlin), F.R.C.S. (Edin.), F.R.C.O.G., F.A.C.S., F.N.I. Foreword by Professor Dr. Robert Schroeder. (Pp. 93+xix; illustrated. 48s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

That very few British gynaecologists have followed Schauta in tackling the surgical treatment of cancer of the cervix by the vaginal route is probably due to the influence and practice of Victor Bonney, who preferred the radical abdominal operation advocated by Wertheim. The end-results of the two approaches are said to be very similar, and eventual resort to a combined abdomino-vaginal operation was inevitable. This step was taken by Professor Mitra in Calcutta over 10 years ago, and in this monograph he details his present technique and his findings and results in 216 cases. Of these, 114 were stage 1, 80 stage 2, and 22 stage 3. The primary mortality rate was 3.6%, and there were no ureteric fistulae.

Mitra attacks the growth first through two inguinal incisions, by way of which the pelvic nodes are dissected out, the ovarian and uterine vessels ligated, the ureters dissected out except for their lowest inch, and the parametria partially mobilized—all extraperitoneally. After closure of the abdomen, radical vaginal hysterectomy is performed with massive removal of the parametria, and a special stitch is inserted to support the bladder. Post-operative supervoltage radiotherapy is given routinely to all patients with parametrial or nodal involvement.

The publisher's American Lecture Series are well known in Britain as elegant — and expensive — productions, but this volume suffers from a surprising number of misprints. Nevertheless, Mitra's monograph is assured of a place on the bookshelf of the gynaecological surgeon, even if the latter has not the thorough

training and regular experience of radical pelvic surgery which the author rightly regards as prerequisites for anyone who would follow his methods.

S. BENDER.

CAHAL'S STUDIES

Studies on Vertebrate Neurogenesis. By Professor Santiago Ramon y Cajal. Translated by Lloyd Guth, M.D. (Pp. 432 +xiv; illustrated. £5 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Cahal is well known in circles outside neurology as the most distinguished Spanish man of science of this century and for the histological techniques which he developed. As a neurologist his standing remains extremely high a quarter of a century after his death. These articles, first published between 1889 and 1925, were issued in collected form in French in 1929. Their translation into English may be regarded partly as an act of justified piety, but also as a real service in making available work that might otherwise be difficult of access.

Through a style which was outmoded even when he wrote, Cahal's virtues show clearly. Careful and critical in observation and trenchant in the expression of opinion, he is as severe with himself as he is with others. Above all he is always conscious of the general implications of problems which, on the face of it, have only a limited interest.

Of the subjects dealt with in these articles it is striking that where Cahal was most definite in his opinions subsequent work has usually confirmed them. Thus he was an early and determined adherent of the "monogenetic" or outgrowth theory of fibre formation, and was right; but a hesitant supporter of a mesodermal origin of Schwann cells, in which he was probably wrong. Apart from neural histogenesis the book contains sections on peripheral endings, the embryonic spinal cord, the cerebellum, the cerebral cortex, and the retina. All contain accounts of original observations, mostly accompanied by critical comments on the literature of the time.

D. R. NEWTH.

APHASIC PILGRIM'S PROGRESS

Stroke. A Diary of Recovery. By Douglas Ritchie. (Pp. 174. 12s. 6d.) London: Faber and Faber. 1960.

This is the victim's account of right hemiplegia with aphasia at the age of 50 and of a three-year pilgrim's progress towards recovery. It is given with admirable candour and liveliness. The liveliness flags a little when the narrative dwindles to diary notes but is fully regained before the end; the candour never fails. It is a most instructive and thought-provoking tale.

The self-observing self, though ill served by the damaged brain and fogged for a short time, never doubts its own existence or seems in danger of perishing. The extreme difficulties of early management are made clear. When nothing comes out it is hard to believe that anything goes in or is going on inside. When "the indwelling word cannot be uttered" how can we tell it is indwelling? Yet here it was. Loud speaking as to the deaf, or baby-talk as to the speechless infant, are wide of the mark. How and when should we try to convey the hard but necessary truth that we cannot cure but only direct and help towards recovery, which depends ultimately on sustained efforts of faith and will by our patient; and will this truth, if conveyed, provoke not effort but suicide?

Mr. Ritchie warmly acknowledges help from many quarters—his wife, his consulting physician, the Medical Rehabilitation Centre in the Camden Road, and his speech-therapist being chief among them. At times he badly needed a medical interpreter, and the continuous care and support of a family doctor failed to flower. He was considerably helped by several books, and his own, with its useful hints for hemiplegic and aphasic patients, should help fellow sufferers as well as medical readers ready to learn from patients.

L. W. BATTEN.

GERIATRIC SURGERY

Management of the Aged Surgical Patient. By Sidney E. Ziffren, M.D. Chapters on *Anesthesia* by Stuart C. Cullen, M.D., *Urology* by Rubin H. Flocks, M.D., and a discussion on *The Cardiac and Diabetic Patient Facing Emergency Operation* by Raymond F. Sheets, M.D. (Pp. 219; illustrated. 57s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

In our ageing population the management of old people before, during, and after operation grows in importance. Old people have their own special disease processes which present particular problems of diagnosis and treatment; and in diseases which are not peculiar to old people the symptomatology may differ from that seen in younger people—for example, acute appendicitis, where the clinical picture can be quite misleading. But the most important condition affecting old people lies in their reaction to the trauma and stress of operation, which may have effects quite out of proportion to those seen at earlier ages. They are more sensitive to minor degrees of blood loss, to changes in blood-pressure and electrolyte shifts, and, of course, they are much more liable to cardiac and pulmonary sequels, to urinary retention, pressure sores, thrombophlebitis, and other complications.

This book deals with all such matters, and there are chapters too on anaesthesia, on the acute abdomen, and on miscellaneous lesions peculiar to the aged. The author's approach is conservative and well balanced, and it is clear that he writes from a good deal of personal experience. It is reassuring to find that he stresses the danger of excessive zeal, whether applied to administering electrolytes or to tackling unresectable cancers. And he has some sage advice about loneliness, boredom, and apathy, which he describes as the three enemies of the aged patient.

C. F. W. ILLINGWORTH.

CARDIAC PATHOLOGY

Pathology of the Heart. By S. E. Gould, M.D., D.Sc. Foreword by Howard T. Karsner, M.D. Second edition. (Pp. 1,138+xvi; illustrated. £13.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The first edition of this book in 1953 was greeted with enthusiasm for its authoritative, superb presentation, and with frustration that it was indeed confined to the heart. Professor Gould and his nineteen collaborators have now remedied this and the new edition properly takes the subject beyond the aortic and pulmonary valves in two new excellent chapters, one on the aorta by Professor Ira Gore and the other on cardiopulmonary disease by Professor Liebow.

The conducting system of the heart is no longer beyond the scope of routine pathology and the splendid new chapter on the subject by Professor Maurice Lev is a most welcome addition, though many pathologists may wish for more help in securing successful histology. Another valuable new chapter is by Professor McManus and Dr. Guerrero on histochemical procedures; the techniques are well selected, and clearly described. The fifth new chapter, on the

surgery of the heart, by Professor Charles Bailey and Professor Joseph Imbriglia will doubtless add to the appeal of this edition by reminding us of the fascinating enterprises of modern cardiovascular surgery. Apart from the authors of the five new chapters, the book retains the distinguished contributors to the first edition; their chapters have been brought up to date (1958) and reset in smaller type; the double-column page is preserved, with the disadvantage that this sometimes makes subdivision awkward. Professor Jesse Edwards deals, as before, with congenital malformations in a masterly section of some 200 pages.

Illustration is profuse and excellent throughout, but the colour plates pairing with Figs. XV.37 and XV.39 are superfluous, and Fig. III.28 could also be deleted without loss. Bibliographies are comprehensive; and misprints are virtually absent—"venosus" (p. 269) and "brain" (p. 872) were the only two noted. The index is a little disappointing—for example, anomalous right subclavian artery is not listed.

Undoubtedly this book is the most complete and authoritative work on the subject in the English language. It is also the heaviest (6½ lb.) and the most expensive (£13). Inevitably there is overlapping, several conditions being dealt with twice or more; even so, one would like some elaboration of subjects like disseminated lupus, carcinoid heart disease, and spondylitic aortitis. Not everyone will agree with the summing up of the aetiology of calcific aortic valve disease nor of cardiac myxoma.

All engaged in cardiovascular work must have access to, if not possession of, this fine book. Professor Gould and his colleagues are to be congratulated, as are the publishers. May one hope for some reduction in the size and cost of future editions by closer integration of the contributions, and possibly some vigorous pruning, especially of non-pathological material?

R. E. B. HUDSON.

John Langton, who died in 1910, compiled the index for the first thirty-one volumes of the *Transactions of the Medical Society of London* because, he said, though it contained valuable contributions to medical science, he thought these were "in the condition of an unworked mine which needed only systematic labour to make its buried treasures available for the common good." The treasures of the present volume of *Transactions* running from October, 1958, to May, 1959, are by no means buried, though some are necessarily more sparkling than others. The Lettsomian Lectures on "Sense and Sensibility," for instance, do not compete with the opening of a discussion on "Carcinoid Tumors"—the facets are simply cut for a different purpose. The Presidential address on "Trends in Medicine 1939–1958" gives an attractive feeling of perspective to a volume that covers the value of routine checks, obesity, malingering, life in a hot climate, the practice of dermatology—for connoisseurs of the irresistible imperative this communication demands that you should "consider the dermatological hazards of Nomadic tribes, particularly in the Middle East"—collagen disease, cerebral arterial disease, and the Annual Oration: "Our Benefactors"—a fascinatingly diverse collection of men and women. The clinico-pathological meeting is noted but no more. Even so, it whets one's curiosity and makes one wish that the *Transactions* could have included pictures of "*X*-ray Appearances of the Spine of a Mummy, Two to Three Thousand Years Old" or "300 Year Old Arawak Indian Skull (Flatted Frontal part due to head binding in infancy)." (The Medical Society of London; pp. 193+lxi; index.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Complications in Surgery and their Management. Edited by Curtis P. Artz, M.D., F.A.C.S., and James D. Hardy, M.D., F.A.C.S. With contributions by sixty-nine authorities. (Pp. 1,075 +xliv; illustrated. £8 1s.) Philadelphia and London: W. B. Saunders Company. 1960.

Theoretical and Practical Problems of Medicine and Biology in Experiments on Monkeys. Edited by I. A. Utkin. Translated from the Russian by Ruth Schachter, M.Sc. (Pp. 276+vii; illustrated. 63s.) Oxford, London, New York, Paris: Pergamon Press. 1960.

Diabetes Mellitus. A Clinical and Pathological Study of 2,529 Cases. By E. T. Bell, M.D. (Pp. 67+viii; illustrated. 30s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

Delinquent and Neurotic Children. A Comparative Study. By Ivy Bennett, M.A., Ph.D. (Pp. 532+xii. 45s.) London: Tavistock Publications. 1960.

Preparing for your Baby. Advice for all Expectant Mothers including Relaxation and Exercises for Natural Childbirth. By Dr. Raymond Gerard Cross and Dr. Dermot Roden. (Pp. 27; illustrated. 5s.) Dublin, Belfast, and London: C. J. Fallon Ltd. 1960.

A Short Guide to Social Survey Methods. (Pp. 24. 2s. 6d.) Published for the National Old People's Welfare Council by the National Council for Social Service (Inc.). 1960.

The Year Book of Medicine (1960–1961 Year Book Series). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. (Pp. 740; illustrated. 60s.) Chicago: The Year Book Publishers. London: Interscience Publishers Ltd. 1960.

Mental Retardation in Infants and Children. By Abraham Levinson, M.D. (deceased) and John A. Bigler, M.D. (Pp. 308; illustrated. 60s.) Chicago: The Year Book Publishers. London: Interscience Publishers Ltd. 1960.

Advances in Internal Medicine. Editors William Dock, M.D., and I. Snapper, M.D. Volume X. (Pp. 390; illustrated. 79s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1960.

Internal Medicine. A Physiologic and Clinical Approach to Disease. By Robert P. McCombs, B.S., M.D., F.A.C.P. Second edition. (Pp. 750+xxiii; illustrated. 79s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1960.

Radioactive Isotopes in Biochemistry. By Engelbert Broda. With a Preface by G. de Hevesy. (Pp. 376+x; illustrated. 57s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

Emotion. A Comprehensive Phenomenology of Theories and their Meanings for Therapy. By James Hillman. (Pp. 318+x. 40s.) London: Routledge and Kegan Paul Ltd. 1960.

Family and Class in a London Suburb. By Peter Willmott and Michael Young. (Pp. 187+xiii. 21s.) London: Routledge and Kegan Paul. 1960.

Grundriss der Medizinischen Mykologie. By Dr. med. Georg Schabinski. (Pp. 183+viii; illustrated. DM. 34.20.) Jena: Veb Gustav Fischer Verlag. 1960.

Die Operative Gallengangsendoskopie. By Prof. Dr. med. Hans Wildegans. (Pp. 105+iv; illustrated. DM 36.) Munich, Berlin: Verlag von Urban und Schwarzenberg. 1960.

Augenheilkunde. Ein Lehrbuch für Studium und Praxis. By F. Rintelen. (Pp. 455+xxvii; illustrated. S.Fr. 65.) Basle, New York: S. Karger. 1960.

Malaysian Parasites XXXV-XLIX. Edited by W. W. Macdonald. Studies from the Institute for Medical Research, Federation of Malaya. (Pp. 251+vii; illustrated. No price.) Printed at the Government Press by B. T. Fudge, Government Printer, Federation of Malaya. 1960.

A Handbook of Tropical Diseases with Treatment and Prescriptions. By J. C. Banerjea, B.M.(Cal.), M.R.C.P.(Lond.), and P. B. Bhattacharya, M.B., D.T.M.(Cal.). Sixth edition. (Pp. 515+xi; illustrated. £2 5s.) Calcutta: Academic Publishers. 1960.

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PREVENTION OF DENTAL CARIES

The theory of the mechanism of dental caries which is still most generally accepted is based on that first propounded by W. D. Miller over sixty years ago. According to this theory enamel caries is essentially a process of decalcification due to acid formed by oral bacteria from fermentable carbohydrate debris left round the teeth after eating. Especially during the last twenty years some research workers have ascribed a more significant role in the carious process to the breakdown of the organic matrix of the enamel or to a chelating action by various substances on the inorganic part. As there is little certain knowledge, in contradistinction to theories, about the mechanism of the carious process in the dental enamel, any preventive measure advocated must be regarded as empirical, though most preventive measures can be explained according to Miller's classical theory.

Unfortunately there is little precise knowledge, based on well-controlled studies, of the value of most of the generally accepted methods for preventing caries. In part, such investigations have been restricted by the lack of cheap experimental animals which develop carious lesions similar to those which occur in man; indeed, few animals develop caries unless they are fed on highly artificial diets. Clinical research on the effects of preventive measures in man have been handicapped by the difficulties in adequately regulating the conditions in the experimental and control groups over the necessarily long period of the investigation. In addition, the clinical assessment of whether a carious lesion is present may be largely subjective, and even an experienced observer may differ significantly in his assessment of caries at two clinical examinations of the same mouth.

Experiments with "germ-free" animals have shown that the presence of micro-organisms is essential in the carious process. However, preventive measures based on the destruction of the bacteria thought to be responsible for caries are either ineffective or, when temporarily effective, as with antibiotics such as penicillin, may cause undesirable allergic and other side-effects and encourage development of resistant strains.

Many investigations have shown that restricting the intake of quickly fermentable carbohydrates, especially sticky ones, is effective in reducing caries incidence. Of special value were the careful studies carried out on groups of patients in a Swedish Mental Hospital.[1] This investigation, and a more recent one on West Tennessee schoolchildren,[2] have shown that frequent eating between meals is especially harmful. Comparison with the results of other investigations in which the amount of fermentable carbohydrates consumed was varied[3,4] strongly suggests that the frequency of eating between meals is more significant than the quantity of fermentable carbohydrates consumed. This is confirmed by the common clinical observation of the exceptionally high susceptibility to caries of people who ingest sweets and sugars for much of the day: this is apparent in babies who have been given sugar dummies to suck and in men and women who, on giving up smoking, alleviate the craving by frequent sweet-eating.

Though cleaning the teeth by tooth-brushing is a generally accepted method for caries prevention, there are few well-controlled investigations[5] which show any distinct beneficial effect and some[3,6-8] which show little or no effect. This apparently contradictory evidence may be due to the need for tooth-brushing to be performed efficiently if it is to be effective in preventing caries. Certainly it must be done immediately after meals by means of a correct technique, and with a properly designed tooth-brush bearing fine, resilient bristles. Tooth-brushes are apt to be used until they can no longer be expected to clean the teeth thoroughly. The rather limited value in preventing caries of most tooth-brushing is not surprising, moreover, because the diameters of most tooth-brush bristles are too great to allow them to reach the sites of many initial carious lesions, such as the depths of the fissures or the confined spaces between the teeth. A minority of dentists believe that tooth-brushing badly performed may actually increase the caries incidence of certain sites on the tooth surface. The removal of food debris by rinsing the mouth with water after meals is a logical supple-

[1] Gustafsson, B. F., *et al.*, *Acta odont. scand.*, 1954, **11**, 232.
[2] Weiss, R. L., and Trithart, A. H., *Amer. J. publ. Hlth*, 1960, **50**, 1097.
[3] Mansbridge, J. N., *Brit. dent. J.*, 1960, **109**, 343.
[4] King, J. D., Mellanby, M., Stones, H. H., and Green, H. N., *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, 1955, No. 288.
[5] Fosdick, L. S., *J. Amer. dent. Ass.*, 1950, **40**, 133.
[6] Weisenstein, P., Radike, A., and Robinson, H. B. G., *J. dent. Res.*, 1954, **33**, 690.
[7] Hein, J. W., ibid., 1954, **33**, 708.
[8] Savara, B. S., and Suher, T., ibid., 1955, **34**, 870.
[9] Hill, T. J., *J. Amer. dent. Ass.*, 1959, **59**, 1121.
[10] Muhler, J. C., and Radike, A. W., ibid., 1957, **55**, 196.
[11] Keys, F. M., Overton, N. J., and McKean, T. W., *J. dent. Res.*, 1960, **39**, 697.
[12] Hagan, T. L., Pasternack, M., and Scholz, G. C., *Publ. Hlth Rep. (Wash.)*, 1954, **69**, 450.
[13] Jenkins, G. N., *Brit. dent. J.*, 1955, **99**, 249.
[14] Dobbs, C. G., ibid., 1957, **103**, 267.
[15] Toverud, G., *Milbank Memorial Fund Quarterly*, 1956, **34**, 354.
[16] —— ibid., 1957, **35**, 127.
[17] —— ibid., 1957, **35**, 373.
[18] Mellanby, M., *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, 1934, No. 191.

mentary method of preventing caries, but little research has been undertaken to indicate its value. It should not be forgotten that tooth-brushing is fully justified because it does much to prevent periodontal diseases and is a socially desirable and aesthetically pleasing discipline. Its value as a caries-preventive measure has been unduly emphasized in advertisements by many tooth-paste manufacturers.

The natural cleansing of the teeth at the end of a meal by foods which have a detergent action due to their fibrous consistency and which stimulate a copious flow of saliva (such as apples) is believed to be of value. Unfortunately there is little evidence to confirm this. The elimination of areas in the mouth where food tends to collect by the filling of already carious teeth or by suitable treatment for abnormalities in the positioning of teeth is probably of value in preventing further caries, but again no investigations have yet shown this conclusively.

Topical applications of various medicaments to the teeth have been advocated. Most clinical investigations with topically applied fluorides show that they are of temporary value, but the cost of such treatment by dentists or dental auxiliaries is greater than the cost would have been for reparative treatment of the carious lesions which the treatment prevented. Some of these medicaments can be applied more conveniently by being incorporated in dentifrices or in chewing gum. In the last twenty years claims have been made that dentifrices containing such drugs, some of which have been stated to act as enzyme-inhibitors or as antimetabolites and to adsorb on to tooth surface or on to the dental plaque, have reduced caries incidence when investigated clinically. More recently claims have been made[9 10] that the use of dentifrices containing fluorides, and especially stannous fluoride, reduces the incidence of caries. Most of these clinical trials with stannous fluoride dentifrices appear to have been well conducted, and one has extended over a period of three years. They seem to show at least a small reduction[11] in caries, but experience of previous dentifrices containing other supposedly beneficial medicaments suggests it would be wise to await further evidence before accepting these claims fully.

The administration of small amounts of fluorides by means of tablets, by the artificial fluoridation of the water supplies, or by the addition of them to foods has been advocated. Extensive well-controlled clinical investigations carried out in many countries during the last twenty-five years have shown that the presence of fluorides at suitable levels in drinking water usually reduces by between 50% and 70% the caries incidence of teeth which developed during the period of administration. There is some evidence that minor beneficial effects accrue from fluoridation even after the teeth have erupted. The main controversy, therefore, about fluorides is concerned with their safety. The administration of fluorides in amounts considerably greater than the generally accepted level of one part per million in the water in temperate climates is undoubtedly potentially dangerous. However, the kidney, the placenta, and the mammary glands are efficient filters preventing a rise in fluorides to toxic levels in the tissue fluids. In addition the large mass of the bony skeleton will act as a reservoir for the accumulation of fluorides; it is large enough to act as a second line of defence for many years if they are regularly ingested in the small amounts generally advocated. Mortality statistics for groups of common diseases[12] show no significant differences between areas with high and with low levels of fluoride in the water. It would therefore appear that, if any harmful effects develop from the artificial fluoridation of water, they are either very rare or of such a minor nature that they have not been shown to affect the expectation of life. It is difficult to prove conclusively that fluoridation of water at a level of one part in a million is always safe; in the relatively few patients in whom it has been suggested that it has caused harmful effects the evidence has been too vague to be convincing. The literature on the safety of fluoridation has been reviewed by G. N. Jenkins[13] and C. G. Dobbs.[14]

In many countries water supplies are now artificially fluoridated. In the United States alone 36,000,000 people drink water containing one part in a million of fluoride or above. In Great Britain a more cautious approach to fluoridation has been made and pilot studies are being undertaken. Despite a natural impatience to make the beneficial effects on dental caries of fluoridation available to more people, this cautious approach is probably justified. No quick results to determine whether harmful effects do occur can be expected from these pilot studies. If they occur, our knowledge suggests that they will be rare and of a minor nature, will develop slowly, and will first be observed in old people after many years, probably after several decades, of drinking fluoridated water.

During the last two decades evidence suggesting that the diet of the mother and child during the periods of tooth formation and immediately after the eruption of the teeth can help to make the teeth resistant to caries has accumulated from experiments on animals and from studies of caries statistics which include the period of rationing during and after the last war.[15–17] Unfortunately there is little to indicate

the precise nutritional factors which are responsible for the resistance. The classical studies of Lady Mellanby[18] showed that vitamin D is essential for the formation of sound dental structure, but the value of an adequate intake of vitamin D in preventing dental caries is still controversial. It would now be generally accepted that it is only one and not necessarily a major factor in producing caries-resistant teeth. In the present state of our knowledge it is probably wise to advise a diet for expectant and nursing mothers and young children which is varied, which contains a minimum of highly refined and processed foods, and which is adequate in the recognized nutritional factors, including vitamin D, for general health.

There is little doubt that caries can be prevented to a large extent by the elimination of our so-called "civilized diet." Unfortunately, the attractiveness and cheapness of modern refined foods make this an impracticable solution. In future, artificial fluoridation of the water supplies and possibly the use of therapeutic dentrifrices may be shown to be safe and effective measures which could be easily applied on a large scale. In the meantime, the incidence of caries can be reduced by a combination of methods which are acceptable to many people. Especially important are the restriction of eating between meals, thorough tooth-brushing and mouth rinsing, and advice and treatment suitable for the individual patient by dentists experienced in preventive measures.

FURALTADONE CONDEMNED

Nitrofurans are substances with antibacterial activity, of which four are now in clinical use. The best known and longest in use is nitrofurantoin ("furadantin"), used exclusively as a urinary antiseptic. Furoxone ("furazolidone") is recommended for the treatment of intestinal infections, and nitrofurazone ("furacin") as an antiseptic for local application. Finally furaltadone ("altafur") is said to have a systemic action, and has been introduced for the treatment of deep-seated infections, since it is reported to attain concentrations in the blood exceeding those required to inhibit the growth of certain bacteria. Those interested in chemotherapy may have watched this development with a somewhat open mind, both because the available evidence did not suggest that the action of this substance could equal or even approach that of a suitable antibiotic, and because convincing clinical evidence of its efficacy had still to come.

Now some authoritative information on furaltadone is forthcoming in the form of three original papers and a leading article in the *New England Journal of Medicine*. The principal paper, by W. R. McCabe and colleagues,[1] describes both laboratory and clinical studies. The minimum inhibitory concentration of furaltadone for 64 strains of staphylococci varied from 1 to 15, but was usually 3.9 or 7.8 μg. per ml. Slightly higher concentrations were bactericidal, but, if cultures in which this effect was occurring were diluted 10-fold, growth began again immediately. The concentrations attained in the blood were also measured. The usual oral dose is 200 mg. at six-hour intervals, and this produced various levels, but 60% of specimens taken two hours after a dose contained no detectable amount of the drug, nor did 78 and 88% after four and six hours. The mean levels at these times were 2.1, 1.4, and 0.2 μg. per ml., all being below the minimum required to inhibit the growth of the greath majority of staphylococci *in vitro*. The intravenous administration of considerably larger doses naturally produced higher levels, but these again were far from constant. The drug was administered orally to 20 and intravenously to eight patients, all with serious staphylococcal infections; of these, eleven had septicaemia or endocarditis, eight wound infections, and six pneumonia or empyema. The treatment failed in seven, five, and five respectively, and in each of two cases of osteomyelitis and one of meningitis. In the few case histories given there are instances of a serious extension of the infection, a pyarthrosis and a septicaemia, developing actually during treatment. Comparison of the blood levels attained, the sensitivity of the organism, and the clinical result showed that a cause of failure was inadequate concentration of furaltadone to affect the micro-organism. Various toxic effects are described, for some of which it seems unfair to blame furaltadone—a rash in a patient previously treated with novobiocin, a rise in blood urea in one who had had kanamycin, and leucopenia more probably caused by ristocetin. But nausea and vomiting were common, as was eosinophilia, and one patient had a severe reaction accompanied by fever, the causation of which was confirmed by experimental repetition of the treatment.

Of the other papers, that by W. H. Mast[2] describes a single case exhibiting severe toxic effects, beginning with diarrhoea and disturbances of sensation and going on to dysphagia, aphonia, diplopia, and unilateral foot-drop; the patient is now slowly recovering from this "peripheral neuropathy." J. J. Byrne and H. S. Goldsmith[3] tried furaltadone for

[1] McCabe, W. R. Davis, J. C., Andersen, B. R., and Jackson, G. G.; *New Engl. J. Med.* 1960, 263, 927.
[2] Mast, W. H., ibid., 1960, 263, 963.
[3] Byrne, J. J., and Goldsmith, H. S., ibid., 1960, 263, 962.
[4] Ibid., 1960, 263, 975.

preventing post-operative infection of wounds in 50 patients; it had no noticeable effect in this direction and four of the patients developed pneumonia, either staphylococcal or pneumococcal, and one a staphylococcal pyelonephritis, during treatment. As the authors remark, both of these are "organisms for which this drug is supposed to be especially useful." The leading article[4] on these papers in the same issue of the *New England Journal of Medicine* is critical of the attitude of the manufacturers of furaltadone to its toxicity. Referring to an advertisement containing the heading "Minimal Side-Effects," it goes on to say, "More than a year before this advertisement appeared, it was known to the manufacturer that the drug had neurotoxic effects in animals, and it had been suggested that the original generic name furmethanol proposed for the preparation was aptly chosen because of the resemblance of its toxic effects to those of methanol poisoning." Apparently 25 cases exhibiting effects on the nervous system have come to light, and these and various other toxic effects have now been mentioned in the manufacturers' circulars. This article also strongly criticizes the use of furaltadone disks for determining bacterial sensitivity. McCabe and his colleagues found that these did not distinguish between different degrees of resistance, and it is complained here that technicians furnish "meaningless laboratory reports" based on their use, and even suggested that the U.S. Food and Drug Administration should control the distribution of such disks and be responsible for their yielding results of clinical significance.

The lesson to be learned from this is that a chemical which inhibits growth on an agar plate is not necessarily a chemotherapeutic agent. It is to be hoped that laboratories in Great Britain have used these disks, if at all, with rather more awareness of their limitations in indicating therapeutic usefulness. The general conclusion to be drawn from all these disclosures is that furaltadone has much more potential toxicity and less antibacterial activity than appears originally to have been thought. A simple comparison of the concentrations required for antibacterial action and those attainable in the body is discouraging to hopes of any dependable therapeutic effect, and clinical experience has been in accordance with expectation on this basis. If antibiotics had never been discovered we might have had to do our best with this drug, but with an effective antibiotic available for almost any bacterial infection, and certainly for any due to a staphylococcus, it is difficult to picture any present indication for its use.

HOW THE MONEY GOES

It is procedure rather than payments, methods rather than money, with which the new Ministry of Health memorandum on hospital capital spending is concerned. Hospital boards are being asked to look forward for ten years, instead of two or three, in submitting their proposals for capital expenditure, and from next month the cost of individual projects which they can undertake without prior ministerial approval will be doubled, from £30,000 to £60,000. Yet there is no doubt that the boards are to be given a longer purse as well as a longer perspective; instead of the £30m. a year capital expenditure now allocated to hospitals in England and Wales, in a year's time the figure will probably rise to £36m., and in four years' time to £50m. Mr. Enoch Powell, the Minister of Health, has given a rough estimate of £500m. capital spending on the hospitals over the next ten years.

How small, relatively, capital spending on the Health Service (which is mostly accounted for by the hospitals) has been in the past is brought out in an article in the current issue of *Bulletin for Industry*, prepared by the Treasury.[1] Analysing trends in social service expenditure in Britain as a whole by all public authorities, and over the past ten years, the article shows that the share of the Health Service in total capital spending on the social services had gone up only from 7% in 1949–50 to 8% by 1959–60. The share of housing, which accounted for 78% in 1949–50, had fallen to 56% ten years later, but this fall is offset by the expansion in private building. There has been little private capital spending on hospitals during the ten years; and the Government's policy has been to give education precedence over the Health Service in the State's capital programme. Public spending on schools and colleges, which amounted to only 11% of the social services' capital budget in 1949–50, had risen to 33% by 1959–60.

The social services can be divided into what are called transfer payments—that is, those which take money out of one pocket and put it in another—and those which buy goods and services. Into the first group come the national insurance schemes, all other forms of pensions, national assistance, and family allowances. These account for nearly half the total expenditure on current account on the social services in 1959–60. The second group is dominated by education and the Health Service, and, in current expenditure as in capital, the share of education in the total has risen over the decade—from 19.5% to

[1] *Bulletin for Industry*, January, 1961. Information Division of the Treasury.

24.2%—whereas Health Service spending reached its peak (28.5%) in 1950–1, gradually fell to 22.8% by 1958–9, and in 1959–60 was 23.1%.

Will the bigger capital spending now envisaged for the hospitals eventually affect their current expenditure? Will it, that is, mean more beds to be maintained, more staff to pay, which will offset the economies to be achieved by modernization? The Minister of Health evidently does not think so. He has coined the slogan "Fewer beds in newer hospitals," and the shift of expenditure within the Health Service in the rest of this century may perhaps be away from the costly hospital service towards the community and domiciliary services. In the meantime, and within the larger field of the whole social services, we now learn from the Treasury that, though current spending on them in the nineteen-fifties rose by more than the growth in the national income, this was the result of higher pensions and giving more children more education. By comparison, the share of the Health Service in the national income was slightly smaller.

CONVULSIONS IN THE NEWBORN

Convulsions are common in the newborn, in whom diagnosis is particularly difficult. They may signify a grave immediate prognosis, and survivors often show permanent cerebral damage.[1] They are therefore a cause of much anxiety. Professor W. S. Craig,[2] of Leeds, has recently presented the results of a study of convulsions occurring within 10 days of birth in 375 personally observed infants. He estimates that about one infant in every 120–125 live births suffers from convulsive twitchings in the neonatal period. Their grave significance is shown by the fact that 158 (42%) of the 375 infants died and came to necropsy. In 97 of the 158 (over 60%) the cause was a non-infective intracranial change such as haemorrhage, venous congestion, generalized oedema, or sinus thrombosis. Other causes included pyogenic infections both intracranial and extracranial, cerebral agenesis, anomalies of the heart and kidneys, and extracranial haemorrhage in the lungs or adrenals.

Two hundred and sixteen infants survived the neonatal period. In only 38 (17.6%) was the diagnosis proved. The causative disorders included pyogenic meningitis, pyelonephritis, cerebral agenesis, hypocalcaemia, and kernicterus: these can usually be diagnosed during life because of one or more characteristic clinical signs which point the way to confirmatory investigations. For example, in pyogenic meningitis a bulging anterior fontanelle is associated with signs of infection such as grey cyanosis and abrupt loss of weight, and the onset is most often during the second or subsequent weeks of life; in pyelonephritis high fever is common and there are pus cells in the urine; hypocalcaemic tetany should be suspected when an apparently healthy infant begins to have convulsions after an uneventful delivery; kernicterus is always possible when jaundice appears in the premature infant or in association with haemolytic disease of the newborn. Craig also describes a rather typical clinical picture in cerebral agenesis: the convulsions appear about the second day of life, thereafter occurring at frequent but irregular intervals, and they are not influenced by chloral hydrate or phenobarbitone. Asymmetry or unusual configuration of the face or cranium is common.

In the remaining 178 survivors only a presumptive diagnosis was possible, an intracranial disturbance being suspected in 152 (over 80%). Accurate diagnosis is often virtually impossible. Even lumbar puncture may fail to differentiate intracranial haemorrhage from other consequences of anoxia such as cerebral oedema or venous congestion. It is interesting, in view of the frequency with which convulsions are related to fever in older infants, that Craig attributed convulsions in 13 of his cases to hypothermia, whereas not a single infant had convulsions which could be attributed to fever *per se*.

Follow-up studies in 141 of the 152 infants with presumed intracranial disturbance showed an incidence of mental and/or physical handicap in approximately 8%. This was contrasted with an incidence of 3% in 488 infants who had shown signs of post-natal asphyxia but in whom convulsions had not been observed. Craig's patients were last examined between the ages of 3 and 3½ years, so no estimate is given in his paper of the incidence of subsequent epilepsy among those infants who survive convulsions after birth. This information would be of great value and would supplement the long-term study of convulsions which is being undertaken by the Committee of Research in General Practice of the Medical Research Council.[3]

SALARY CRISIS AT CAMBRIDGE

At the end of next week members of the Regent House of Cambridge University will vote on the proposals relating to stipends put forward by the General Board. We have already referred to the controversy which these proposals have aroused.[1] The crux of the matter is whether the University will turn its face against differential salary scales or will accept the need to pay the clinical staff of the medical school the higher salaries the University Grants Committee has authorized.[2] Both sides in this dispute have already made their views plain,[3] but it is customary at Cambridge for advocates on each side to circulate "fly-sheets" before a ballot of the university, and several of these have recently been

[1] Burke, J. C., *Arch. Dis. Childh.*, 1954, 29, 342.
[2] Craig, W. S., ibid., 1960, 35, 336.
[3] Hope-Simpson, R. E., *Brit. med. J.*, 1960, 2, 1023.

distributed among those entitled to vote. In one of them Professor J. S. Mitchell, the Regius Professor of Medicine, points out how very difficult it will be to continue the development of the School of Clinical Research and Postgraduate Medical Teaching if differentials are abandoned, and he emphasizes the necessity for maintaining the principle of whole-time appointments without private practice. Professor G. M. Trevelyan, O.M., takes a firm stand alongside those who support differential salaries, stating that a first-rate research school of medicine at Cambridge—important both for Cambridge and for England—can be obtained only if the salaries are fixed high enough in relation to the circumstances of the medical profession. Lord Adrian, O.M., joins with numerous other distinguished signatories to urge the university to accept substantial differentials in favour of clinical departments: they support the Regius Professor in stating that the demands of private practice are not compatible with the duties of a university officer. Further, they believe that candidates for teaching posts cannot fail to be influenced by the scale of stipends offered by other universities and by the National Health Service. In that connexion another fly-sheet signed by a number of consultants at Addenbrooke's Hospital, who are also associate lecturers in the Faculty of Medicine, asks: "If clinical differentials are not accepted how can the medical school hope to attract first-class individuals to its teaching staff when the scales of pensionable stipends offered will be in some instances more than 30% below those obtaining at other medical schools?"

Among those who oppose differentials on principle there are some who think that university teachers with additional clinical responsibilities should receive additional payment from "extra-university sources." Some members of the medical faculty, along with other Cambridge teachers, have suggested that the difficulty might be overcome by paying the staff of the postgraduate school of clinical medicine the same stipends as other teachers, but leaving them free to accept any payment offered by the National Health Service in recognition of their responsibilities to the hospital. Alternatively, the clinical staff might be employed by the N.H.S. but possess the status of honorary university teaching officers. Somewhat similar suggestions have been made by several of those who have joined in the correspondence on the subject in this journal, one writer[4] making the additional point that the work of some preclinical teachers is also a direct contribution to the Health Service, though no recognition is given to this.

The matters of principle raised in the General Board's report on stipends have now been very thoroughly debated, and those entitled to vote cannot but be aware that the future of the Cambridge Medical School may well lie in their hands. If, as a result of this ballot, other universities are going to be able to offer to clinical teachers salaries 30% higher than those at Cambridge, the Medical School there is bound to suffer—particularly the development of the school of clinical research and postgraduate teaching, which the council of the Senate has already approved—and the harm that this could do would extend far beyond Cambridge.

[1] Leading article, *Brit. med. J.*, 1960, 2, 1579.
[2] See *Supplement*, ibid., 1960, 2, 216.
[3] *Cambridge University Reporter*, November 3 and 23, 1960.
[4] Allwood, M. J., *Brit. med. J.*, 1960, 2, 1881.

BRUCELLA PUZZLES

Recently four members of the staff of the Mayo Clinic[1] have described 36 cases of *Brucella* infection in the bones and joints, a condition which has received more attention in the United States than in Great Britain. If, as the authors suggest, the possibility of *Brucella* infection were borne in mind in all cases with inflammatory disease of the bones, joints, or bursae, it seems certain that more evidence of such infection would come to light—especially infection of the spine, in view of the frequency of severe pain in the neck and back in undulant fever.[2] Although *Br. suis* is usually considered to have the greatest affinity for bone, yet of the 22 culturally proved cases in the Mayo Clinic series only eight were due to this organism, *Br. abortus* having been found in eight cases and *Br. melitensis* in four, the species not being determined in the remaining two cases.

But it is not only in bone and joint cases that *Brucella* infection is apt to be missed, or, if suspected, too hastily laid aside. It is true that the manifestations of undulant fever are bewildering in their variety, but the fact that in Dalrymple-Champneys's series of 1,500 cases[3] the most frequent provisional diagnoses were influenza (159 cases) and typhoid or paratyphoid (115 cases) gives a general idea of the picture most usually seen. In such a disease clinical diagnosis can only be very provisional, though experience teaches the physician what to expect. It is worth remembering that, quite apart from the acute cases, there are many in which the initial illness has been overlooked or given some such label as "feverish cold," but which have settled down into a condition of chronic ill-health with banal symptoms and no physical signs, and have all too often been labelled "neurosis."

If the fever lasts long enough, an undulant type of temperature chart will usually appear. Heavy sweating is the commonest sign in this disease, but in most cases eventually diagnosed it is the continuance of fever with an almost complete absence of physical signs which suggests the possibility of undulant fever. Unfortunately in many cases the correct diagnosis is then discarded on the strength of a negative agglutination test, though agglutinins often take some time to appear, if they appear at all, and the presence of incomplete or blocking antibodies may interfere with the test. Finally, culture from the blood, sternal marrow, urine, etc., is too seldom attempted, and then sometimes with faulty technique.

[1] Kelly, P. J., Martin, W. J., Shirger, A., and Weed, L. A., *J. Amer. med. Ass.*, 1960, 174, 347.
[2] Dalrymple-Champneys, W., *Brucella Infection and Undulant Fever in Man*, 1960, p. 74. Oxford University Press.

Clinicopathological Conference

A CASE OF EXERTIONAL DYSPNOEA

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a middle-aged man, with a history of rheumatic fever and syphilis, who developed exertional dyspnoea, followed by renal and hepatic complications (Case No. 238,219; P.M. No. 9,172).

Clinical History

Dr. C. L. COPE: The patient we are considering to-day was, when he died, a widower aged 51. He had had many jobs, including painting and decorating and factory work, and was at the time of his illness a Post Office messenger. He entered Hammersmith Hospital on March 9, 1960.

At the age of 7 he had rheumatic fever, spending two months in bed. A recurrence had occurred at age 24 when he spent six weeks in hospital. Subsequently he appears to have had a very good exercise tolerance. He played football when young and passed a life insurance examination without loading. At age 32 he had serum jaundice after antisyphilitic treatment. His present illness began in September, 1959, with fairly rapid onset of breathlessness on effort. Several possible causes for such a symptom will come to mind, and it is relevant that he experienced no cough, no chest pain, no fever, no palpitations, and no nocturnal dyspnoea. There had been no syncope and he slept with two pillows at night.

In November, 1959, he had an attack of, what I think is uncommon these days, facial erysipelas, and he was treated with penicillin at home. It cleared up quite rapidly and he returned to work. Soon after that he developed a complaint which was called by his doctor mild bronchitis, and it is an open question, I think, what that was. It could have been left ventricular failure, but we do know that the sputum became thick and brown in colour. At this time his dyspnoea on exertion was progressively worsening and finally forced his admission to another hospital in January, 1960. When he went in he was very dyspnoeic, but there was no chest pain and no oedema. He was considered to have heart failure and was treated with digoxin, diuretics, a low-salt diet, and expectorants. A diagnosis was made at that other hospital of aortic stenosis and aortic regurgitation. Three weeks after admission to that other hospital he developed cramp in both calves, more marked in the right than in the left, and both, especially the right, became swollen and mildly tender. He was thought to have thromboses and was treated with "dindevan" (phenindione) as anticoagulant. Soon after that he developed a severe aching and stabbing pain in the epigastrium which was mildly aggravated, he thought, by food. But the association wasn't a close one, although he himself insisted that food had some effect on it. The oedema of the legs had then subsided and he was discharged home on February 8.

When he got home he was still very short of breath; he needed two, and occasionally three, pillows at night. He still had a sharp pain—he described it as "stabbing"—high up in the epigastrium, still associated with, or aggravated by, food. Then he started to vomit. The vomiting became more frequent and for this he attended as an out-patient at his hospital and was given chlorpromazine, which he continued to take for about a month. In addition, he continued to take as an out-patient the anticoagulants that had been started while he was in hospital together with chlorothiazide and hydroflumethiazide occasionally. So he was on a lot of drugs. He got worse, especially from the point of view of the pain in the abdomen and the dyspnoea, which was already severe. The pain had produced vomiting, and the vomiting had increased and was really becoming a major feature. Mainly because of the pain and vomiting he was admitted to Hammersmith Hospital.

ON ADMISSION

When he came in here he was very ill, retching frequently and bringing up small amounts of gastric juice. He was pale and distressed. He had no fever. The distress appeared to be in large part due to the pain he had in the epigastrium. He was slightly confused, and with that he had some anxiousness, which is not surprising. Dyspnoea was mild at rest; his respiratory rate was 22 and he was not orthopnoeic. His pulse was regular at 100; he was not fibrillating. Because of the vomiting he was appreciably dehydrated. He appeared to have some peripheral shock, too, for he had cold extremities and his blood-pressure was low, 100/50, and, incidentally, remained at about that level thereafter. He had a raised jugular venous pressure up to the angle of the jaw with considerable fluctuations in it probably, though it was difficult to sort that out from a very pulsating carotid artery with a Corrigan pulse which he had at that time. In the heart he had a triple rhythm at the apex and a moderate enlargement. There was an aortic systolic murmur and a thrill and an aortic diastolic murmur which was early and high-pitched. The pulse was thought by several people to be slow-rising with a rapid fall, and all his peripheral pulses were palpable. So there was strong evidence that he had aortic regurgitation and some evidence that he had aortic stenosis. In the lungs there was slight dullness at the right base only and crepitations at both bases and that was all. These were mild pulmonary signs and not remarkable at that time. There was no clubbing and no cyanosis. In the abdomen at the time of admission his liver was enlarged three fingers down, was markedly tender to palpation, and when it was pressed on very firmly a pain was produced which he said was very similar to the epigastric pain that had been such a feature when it had occurred spontaneously. The liver, when he came in, was pulsating also. We thought at the start that he was slightly icteric. It was very slight, and, as you will see later, his bilirubin on admission was about 2 mg. His spleen was not felt and there was nothing else remarkable in his abdomen. He had no petechiae and no evidence of systemic embolism.

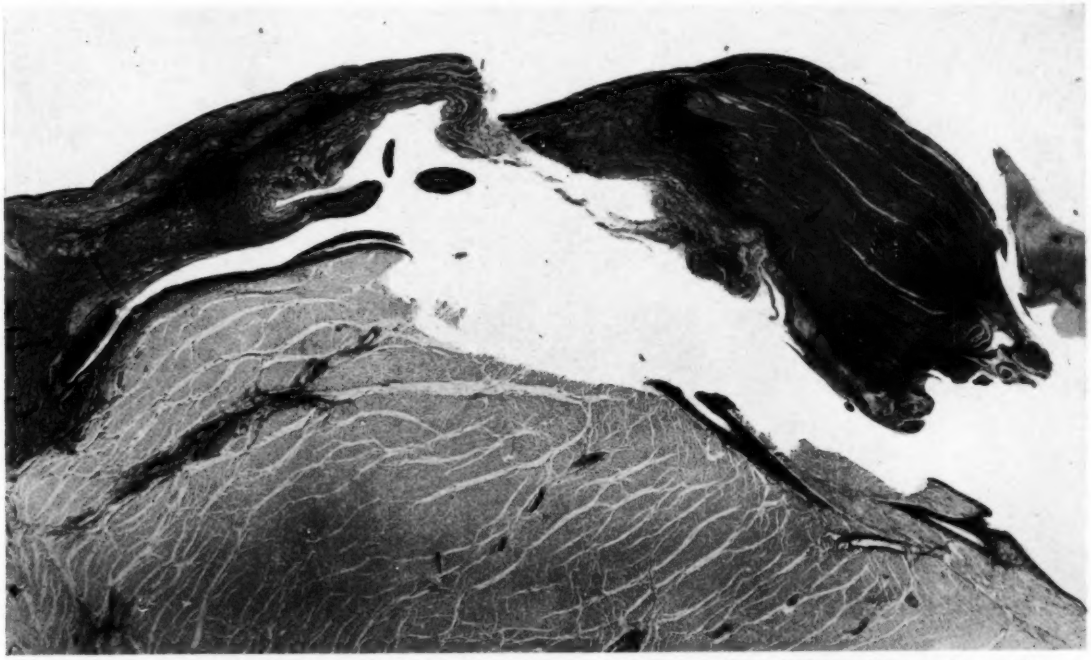

FIG. 1.—Mitral valve showing fibrous thickening most marked near its free margin. (Elastic/van Gieson stain. ×15.)

FIG. 2.—Pulmonary artery occluded by impacted embolus. Some of the loosening at the periphery is due to organization. (Haematoxylin and eosin. ×56.)

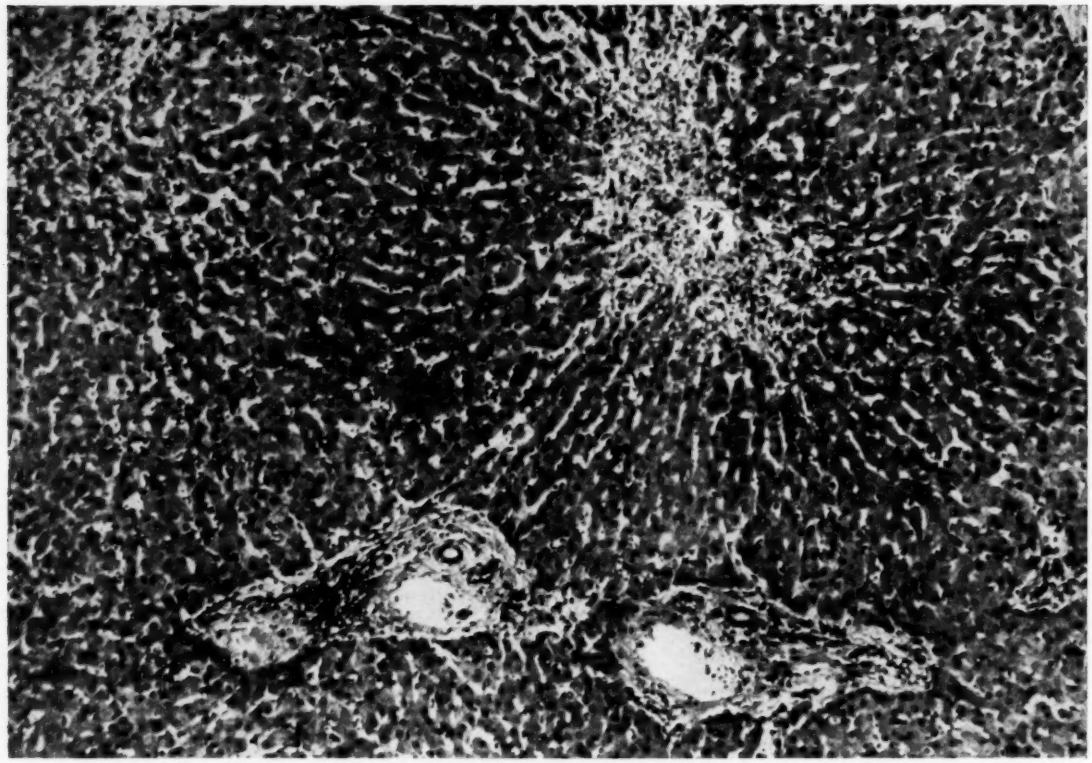

FIG. 3.—Liver showing destruction of liver cells around centrilobular vein (towards upper right) and cellular infiltration of portal tracts (towards bottom). (Haematoxylin and eosin. ×100.)

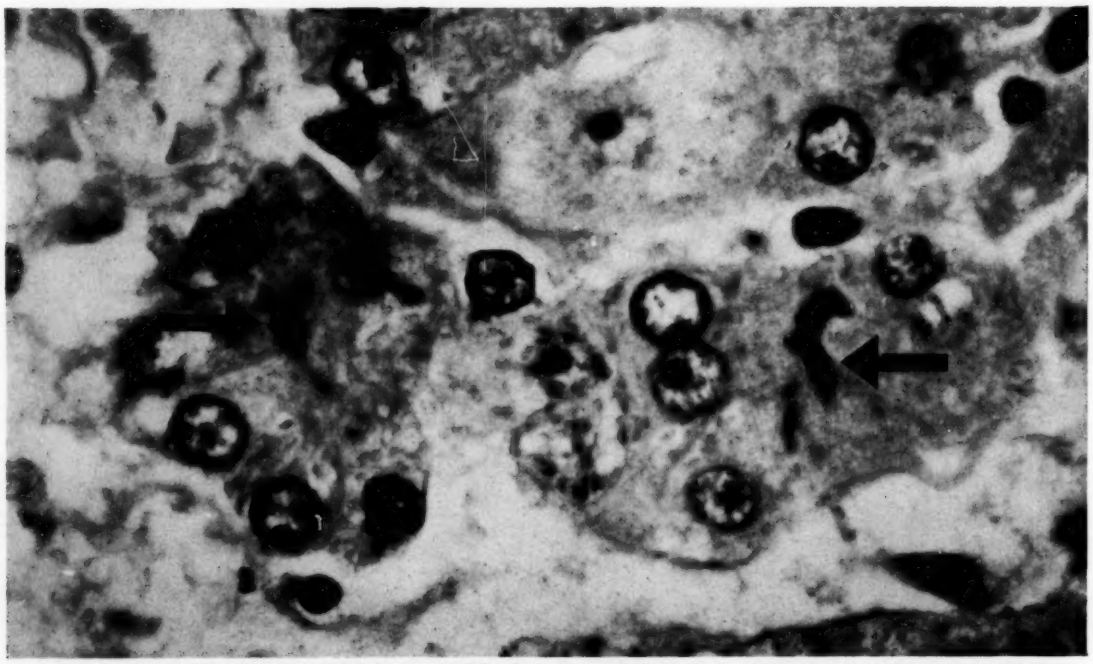

FIG. 4.—Liver cells near centre of lobule showing bile plugs in canaliculi (arrows). (Haematoxylin and eosin. ×1,450.)

INVESTIGATIONS

A number of investigations were done. He had albuminuria ++ which persisted most of the time subsequently. There was nothing remarkable otherwise in the urine; there were no red cells, no pus, and no casts were seen. His haemoglobin was 12.3 g., probably higher than it should have been because of the dehydration—in other words, he was probably more anaemic than that. He had a leucocytosis of 15,000, but only 73% polymorphs. His urea was well up at 141 mg. at that time, which could have been due to the severe dehydration, but probably had other causes as well. Sodium was not grossly low at 130 mEq, the normal being about 135 for our hospital patients. Bicarbonate was reduced at 18 mEq; potassium 5.6 mEq; chloride normal; bilirubin 2.1 mg. Van den Bergh positive. Plasma proteins not remarkable. Transaminases raised—both the oxalacetic and the pyruvic—370 and 380 units/ml. respectively. An E.C.G. showed moderate left ventricular hypertrophy but no evidence of ischaemia. A radiograph of his chest showed what was described as "enlargement of all chambers, with a slight shadow at the left base which might have been a patch of consolidation and might have been a small infarct." That is what the report actually said.

SEVERE OLIGURIA

When he came in he was severely ill. He was able to retain some oral fluids, but after a day or so it was noticed that he had a very severe oliguria. He also had mild ankle oedema which came on soon after admission, and it became apparent that he was getting more jaundiced. For the first few days after admission his urine volume was around 400 ml. daily and it was of low specific gravity. He became slowly more drowsy and occasionally non-rousable, and even when he was roused he was very remote and difficult to make contact with. His oedema increased slightly, though it was never a gross feature. Crepitations persisted at both bases and did not change remarkably whilst he was in.

Then on March 13, four days after he came in, his stools became clay-coloured and it was also found at that time that his serum sodium had fallen very considerably and was now 117 mEq. We were faced then with a man with a low serum sodium and oedema, and we had the problem of whether or not we ought to give him salt. The only feasible course was to give him some and see what would happen, and that was done. He had about a litre of sodium lactate and it improved his serum sodium level, but it did not appreciably improve his general condition; it may indeed have aggravated the oedema slightly. So we were fairly sure then that the symptoms he had—the remoteness and the drowsiness—were not largely referable to the low serum sodium. At that time he was also given digoxin as a routine. The next day, March 14, he was still in this light coma and then he developed intermittent breathing of a type which I think is called Biot's breathing—that is, it was of the all-or-none kind, either deep respiration for five or six breaths, or nothing at all, in contrast to the ordinary Cheyne–Stokes, which gradually builds up and then falls off again. He continued to have that for a day or two. At the same time his jaundice was becoming deeper, bilirubin being now 7 mg. His jugular venous pressure was unchanged, still up near the angle of the jaw. The oedema was rather more marked in the legs and now was evident on the sacrum. He still had oliguria, around 400 ml. At this time, too, he developed a flapping tremor of the type which is associated with liver failure, and he maintained that gross flapping tremor for two or three days, and with that he also had a pronounced bleeding tendency whereby he bled persistently from any needle puncture and there was strong reason for not giving him any injections; even taking blood was difficult.

DEEPENING JAUNDICE

Two days later, on March 16, he had a mild increase in urinary volume, which was a considerable relief because we were not sure what was happening to his kidneys. Remember he had deepening jaundice and a rising blood urea. His urine volume rose to about a litre a day, and by that time his blood urea had gone up to 400 mg. Throughout this period he had been on intravenous and occasionally oral fluids and glucose, so he had been getting a fair number of calories in and a reasonable fluid intake. His bilirubin had now gone up to 13 mg., but even with a bilirubin as high as that he still had no bile in the urine. That is an interesting point. His plasma carbon dioxide had returned nearly to normal and he was still semiconscious—in about the same clinical state as he had been before.

On March 19 the condition was similar except that the jaundice was deepening. The bilirubin had risen even higher to 23 mg., but the blood urea was beginning to fall and had now dropped down to 330 mg. In fact, it fell further progressively during the next few days. He was still drowsy, but his liver, which at first had been so large, so tender, and so pulsatile, was no longer either palpable or tender, and we had the strong feeling that it had contracted down and the feeling that there might be some kind of liver atrophy going on in it. Jugular venous pressure was unchanged. The spleen was still not palpable. At about this time pigments returned to his stools, and bile for the first time appeared in the urine. On March 22 the condition was similar except that the jaundice was deepening, but the blood urea had fallen now to 180. His respiration was still only 20, pulse 90. There was no fever, and crepitations that had been heard earlier at both bases were still audible at both bases in similar quantity. On March 24 he died quietly in coma, and we hadn't really a very certain complete diagnosis.

Clinical Diagnosis

(1) Chronic rheumatic heart disease.
(2) Aortic regurgitation and aortic stenosis.
(3) Tricuspid incompetence.
(4) Recovering lower nephron nephrosis.
(5) Acute liver failure due to:
  (*a*) ? subacute liver atrophy.
  (*b*) ? chlorpromazine or other drug.
(6) Pulmonary embolism (? recurrent).

Post-mortem Findings

Professor C. V. HARRISON: The body was that of a well-built man weighing 8 st. 13 lb. (56.7 kg.), height 5 ft. 7 in. (1.68 m.), with some jaundice and scars of old herpes on the left thigh.

The pericardium contained 50 ml. of bile-stained fluid. The *heart* weighed 560 g. (normal, 360 g.). The aortic valve appeared to have been bicuspid and was also heavily calcified so that the orifice was a narrow

slit 23 mm. long. The mitral valve showed fibrous thickening of its margin (Fig. 1) and slight fusion of its commissures, but had a circumference of 85 mm. (normal, 90–110 mm.). The tricuspid valve was a little dilated, 140 mm. in circumference (normal, 130 mm.). The pulmonary valve was normal. Both ventricles were hypertrophied. The coronary arteries had a slightly anomalous distribution but were unobstructed. The myocardium showed a few minute foci of fibrosis. There was a little thrombus in the right atrial appendage and there was a small Chiari's web near the superior venacaval opening. In the aorta there was a small "jet" lesion, but otherwise there was singularly little atheroma. Microscopy confirmed the various naked-eye findings.

Both *lungs* showed haemorrhagic infarcts, particularly in the lower lobes. In the left there was some bronchopneumonia and in the right there was extensive and severe bronchopneumonia. Microscopically these findings were confirmed. Some of the pulmonary emboli (Fig. 2) were old enough to be undergoing organization.

The *liver* was small, 990 g. (normal, 1,500 g.), and showed exaggerated lobular markings. This appeared to be partly due to congestion and partly to bile staining. Microscopically there was obvious passive venous congestion. In addition there were two other features that are not obvious in passive congestion—namely, cellular infiltration of the portal tracts (Fig. 3) and bile thrombi in the canaliculi (Fig. 4). It is possible that these were due to chlorpromazine. There was certainly no mechanical obstruction to account for the biliary obstruction or for the clinical jaundice. The *pancreas* showed a few foci of terminal fat necrosis.

The *kidneys* were of normal size and did not show any macroscopical abnormality. Microscopically there were some casts in the second convoluted tubules and in Henle's loops, indicating a rather mild degree of tubular necrosis.

The *thyroid* was small, 12 g. (normal, 26 g.), but otherwise normal. The *suprarenals* showed cortical hypertrophy, 20 g. (normal, 12 g.).

Pathologist's Diagnosis

(1) Calcareous aortic stenosis of bicuspid aortic valve.
(2) Chronic rheumatic mitral valve disease.
(3) Multiple pulmonary emboli.
(4) Jaundice, probably due to chlorpromazine.

Discussion

Dr. COPE: I will try to sum this up a little. It is not easy, as you see, and there are many ramifications to the case. There are several headings, however, under which I think one can put the main themes. First of all there was the heart, with a history of rheumatism, and with rheumatic valvular disease which had not worried him up to the age of 50, so far as we know, and probably didn't worry him very much after that even during his last year of life, but that may be discussed later.

PULMONARY SITUATION

Secondly, there was the pulmonary situation, which almost certainly accounts for the very rapid deterioration in his exercise tolerance, and here there was early suspicion of pulmonary infarction in the other hospital and we had it ourselves. I think it is fair to say that we didn't realize the extent of the pulmonary infarction that was going on, although we recognized that some was probably occurring. We really underestimated its severity. Why it occurred we don't know, nor for how long it had occurred—probably several months, because you will remember that he was put on phenindione two or three months before he came in to us. He continued on phenindione until the bleeding tendency developed and then, of course, it was unnecessary. So far as one can see from the clinical record and the pathological findings, he continued to have many infarcts, apparently whilst still on phenindione, and possibly still when he had the bleeding tendency right at the end, owing presumably to his liver failure.

RENAL AND HEPATIC FAILURE

The third factor is the renal failure—the rise in blood urea and its subsequent partial recovery. We could only speculate about that. To some extent that was, no doubt, aggravated by dehydration, because you remember he was vomiting just before he came in; but I doubt myself whether the degree of dehydration he had was enough to account for such a severe rise in blood urea. We thought at the time that it might have been due to a shock-like episode which could have arisen from a pulmonary embolus, but, as I said earlier, there was no period in the history where we could recognize a shock-producing incident, so that was a little speculative. But we suspected, and the pathology seems to bear this out, that it was related to a probable period of fall in blood-pressure.

The fourth aspect in this case is the liver failure—perhaps we had better say the jaundice rather than the liver failure. We knew he had pulmonary emboli. We knew he had a high jugular venous pressure and venous congestion, and the association of the two was enough to give him some jaundice and we could have attributed it to that; but it didn't seem to fit adequately because the jaundice got progressively worse right up to the end, and there was certainly no clinical evidence (even considered in retrospect) of large pulmonary infarction going on. His jugular venous pressure changed very little whilst he was in hospital. I doubt very much whether pulmonary infarcts were adequate cause for the severe jaundice. The liver, as you have heard, shrank quite a lot while he was in hospital. Now that could have been due to subsidence of his tricuspid incompetence, with resultant fall in jugular venous pressure and venous congestion; but, in fact, the jugular venous pressure did not fall very much, and we were quite confident that the shrinkage was not explained in that way. It was because of the shrinkage that we suspected some sort of atrophy and suspected also that it might have been associated with the chlorpromazine. I think multiple factors have been active in the liver: possibly two or three factors in the kidney, and possibly several in the pulmonary infarctions as well.

TERMINAL COMA

Professor RUSSELL FRASER: I didn't quite gather, Professor Harrison, why you think he was in coma over the last few days. That was another factor.

Professor HARRISON: I don't know. He had got a remarkably severe and widespread pulmonary infection and he was a sick man with a failing circulation. It's possible that he had a severe toxaemia.

Dr. COPE: Do you think that the bronchopneumonia was all terminal, or do you feel that it must have been

there longer? He had no fever right up to the end, although, as you will remember, he came in with a leucocytosis of 15,000, and blood cultures, incidentally, were negative.

Professor HARRISON: I think that the bronchopneumonia is at least several days old; I wouldn't put it at a week.

Professor RUSSELL FRASER: Bronchopneumonia is a very likely complication in someone in coma from any other cause.

CHLORPROMAZINE JAUNDICE

Dr. J. F. GOODWIN: May I ask a question about the relationship of the chlorpromazine in regard to the interval between its being stopped and the onset of the severe jaundice? I see that on his admission on March 9 the bilirubin was then 2 mg., which would seem to be perfectly consistent with heart failure and pulmonary embolism. Subsequently it went up to 7 mg., which seems, I agree, a little high, but was there not a fairly long interval after stopping the chlorpromazine, and, if so, does this influence the suggestion that he may have had chlorpromazine liver damage?

Dr. C. C. BOOTH: The problem in this case is what his jaundice was due to, whether it was due to heart failure with destruction of liver cells by venous congestion and subsequent shrinking of the liver, or whether it was a chlorpromazine jaundice. Professor Sheila Sherlock wrote up the former type in 1951,[1] studying, I think, 50 cases, most of which had serum bilirubins of up to 5 or 6 mg./100 ml. Only three had serum bilirubins of over 15 mg. In her cases there did not appear to be a progressive gradation from 5 up to 20 mg.; there were just three that had got levels of over 15 mg. One just wonders whether there might have been some other factor in these particular three cases. Dr. Read has had a lot of experience in the chlorpromazine cases.

Dr. A. E. READ: I think the difficulty here is trying to fit chlorpromazine jaundice, which is an obstructive jaundice, in with a small liver. Classically in obstructive jaundice the liver is enlarged. It doesn't matter whether the obstruction is inside the liver or outside the liver, and chlorpromazine jaundice usually gives you an enlarged liver with other signs and symptoms of obstructive jaundice. However, I think very rarely, cases have been recorded in which the obstructive element is sometimes overshadowed by liver-cell necrosis. This isn't a thing which is appreciated very frequently, but one or two patients who have died of chlorpromazine jaundice have shown hepatic-cell necrosis as well as the features of obstruction. I just put it forward that one of the reasons why this liver was small is that part of the necrosis is in fact due to chlorpromazine jaundice. The other thing I find difficult is the fact that there was no bile in the urine. I don't know what sort of jaundice that comes under.

Professor RUSSELL FRASER: Dr. Read, would you like to comment on this question of the time interval in chlorpromazine jaundice?

Dr. READ: The usual period is 10 days to three or four or so weeks from the taking of chlorpromazine. There is a red herring here; I think at necropsy on this patient, which I remember very well, someone said that he had had "stematil" (prochlorperazine) when he came in. Now if he had chlorpromazine first and then prochlorperazine, it may be that the rapid rise in bilirubin on the second occasion was due to cross-sensitivity, which does occur with some of these drugs.

Dr. E. D. WILLIAMS: It certainly was stated at the post-mortem examination that he was given prochlorperazine very shortly after admission. The other point is about the infecting organism. I believe that a culture was taken shortly before death and a pneumococcus was grown.

HEART FAILURE AND PULMONARY INFARCTION

Dr. WILLIAMS: It has been suggested in the literature that people with congestive heart failure are more sensitive to the toxic effect of chlorpromazine, but this was only in a very short article by Boardman in 1954.[2] The liver as described in that case was enlarged, showed a nutmeg pattern, and the microscopical appearances were stated to be those of a toxic hepatitis.

Dr. J. P. SHILLINGFORD: In heart failure alone, although Professor Sherlock showed that in three of her series the bilirubin rose as high as 20 mg., and although one sees jaundice up to 3 or 4 mg., especially after pulmonary infarcts, I should have thought it was very rare to get so much jaundice.

Dr. GOODWIN: I should like, just for the sake of argument, to take the opposite view and say that this man had had so much pulmonary infarction that this really isn't inconsistent, and that if he hadn't been given this unpleasant drug we should have said that this really fitted in very well with heart failure and pulmonary infarction, although the serum bilirubin was perhaps a little bit high for this. I find the chlorpromazine story a little unconvincing.

Dr. I. DONIACH: Can I support Dr. Goodwin on this, because the centrilobular necrosis, which is part of ordinary congestive heart failure, is said to be much exaggerated by pulmonary infarction? Apart from adding a load of bilirubin to be dealt with, pulmonary infarction may be associated with further centrilobular necrosis in the liver, and, in fact, is thought to play a part in the later development of cardiac cirrhosis in some of these people.

BILE IN THE URINE

Professor RUSSELL FRASER: He certainly had all the features that could contribute towards a cardiac jaundice, didn't he? What about the question of bile in the urine, Dr. Cope? This would seem to be rather important.

Dr. COPE: I am not prepared to comment on that, but I understand that somebody has seen this and knows something about it. Is there anyone here who does? Dr. Milne is away, but it has been seen by somebody—a delayed appearance of bile in the urine in people with recovering lower nephron necrosis. Don't forget that there was the renal damage here as well as the liver damage, but I can't comment on it other than that. I don't myself think that the lung infarcts he had were adequate explanation for such an extreme jaundice terminally.

Professor HARRISON: I support Dr. Cope on this. I have seen this extensively in mitral stenosis, where pulmonary infarcts are almost the rule, where you get large numbers very frequently, and you simply don't see this degree of jaundice or this number of bile thrombi in the liver. I think this is an exaggeration of

[1] Sherlock, S., *Brit. Heart J.*, 1951, **13**, 273.

[2] Boardman, R. H., *Brit. med. J.*, 1954, **2**, 579.

what one would expect in a cardiac failure alone, and therefore I would postulate something a little more than merely that.

FLAPPING TREMOR

Dr. COPE: I wonder whether I might ask Dr. Read to comment on the flapping tremor in relation to chlorpromazine? This man certainly had that for two or three days and then it went off. That seems to me inconceivable in a cardiac jaundice, but possible in a chlorpromazine one. Would Dr. Read agree?

Dr. READ: There I support the chlorpromazine story. I think that if this was a hepatic tremor it would merely mirror centrilobular necrosis of liver cells, which could either be chlorpromazine on my side of the fence, or cardiac on the other. I still think this man had chlorpromazine jaundice. As Professor Harrison has shown us, he has two histological features that, I think I am right in saying, you do not get in congestive cardiac failure—namely, considerable cellular infiltration in the portal tracts and many bile thrombi. Whether he had some peculiar response producing necrosis of liver cells as a result of the administration of chlorpromazine, or whether this is just the result of damage from centrilobular stagnation, I think is another question which is very difficult to answer.

Dr. SHILLINGFORD: This man was very jaundiced—very, very jaundiced—and it's seldom that one sees such severe jaundice from heart failure alone, although a slightly raised serum bilirubin is more common.

Dr. BOOTH: It is in fact recorded in the literature, this is the difficulty. I admit that this is a rare phenomenon, but there are three cases amongst those 50 that Professor Sherlock recorded, and you either accept them or you don't.

Dr. SHILLINGFORD: This is the first case that I can recollect having seen with this degree of jaundice in heart failure over the last five or so years.

Dr. COPE: Dr. Shillingford, are we to understand that the three cases recorded in 1951 were not associated with drug administration?

Dr. SHILLINGFORD: I do not know.

Dr. BOOTH: It is not in fact recorded.

Dr. COPE: It is conceivable that the drug association wasn't recognized adequately at that time.

Dr. BOOTH: I quite agree. This is the point, though—in that paper the levels go up to 6 or 8 mg. at the most, and then there is not a gradation up to 20; there is a great jump which of itself might suggest that other factors were involved.

Dr. DONIACH: I should like to clear up one point which has been raised by Dr. Read, and that is the bile thrombi. I am certain I have seen them in the liver in cases of heart failure. I think Professor Harrison will probably agree?

Professor HARRISON: Oh yes, entirely. It's the number of them in this case that is unusual.

SOURCE OF THE EMBOLI

Dr. COPE: I wonder whether we could switch to the pulmonary emboli, which, after all, were an equally important feature. He had large numbers over a long time. We don't know of a definite site of origin for the majority of them. He didn't have any tenderness in his legs latterly. He had, from all the evidence, quite a lot of pulmonary emboli at the time when he was under good anticoagulant control, and quite possibly several at the time when he had a gross bleeding tendency. That might be a matter for comment?

Dr. WILLIAMS: At the post-mortem examination we did express blood from the femoral veins, as he had had this history of calf tenderness. The calf veins were not explored. He did, however—I think I am right—have antemortem thrombus in his right auricular appendage.

Professor HARRISON: That is correct.

Dr. WILLIAMS: So we did find one source, and there was this possibility from the clinical history of further sources in the legs.

Professor RUSSELL FRASER: From the pathology did you have reason to think of them as emboli? They were not like local venous thromboses?

Professor HARRISON: Yes, emboli.

Dr. GOODWIN: There was not a lot of atheroma in the pulmonary tree?

Professor HARRISON: No.

Dr. GOODWIN: So presumably he hadn't had severe pulmonary hypertension for a long time?

Professor HARRISON: No.

AORTIC VALVE

Dr. GOODWIN: This is a very typical history of aortic stenosis, as the patient may be perfecly well until about this age and then suddenly deteriorate with dyspnoea, heart failure, tricuspid incompetence, pulmonary hypertension, and then multiple pulmonary infarcts. I think most of these do come from peripheral sites, although occasionally they do arise from the right atrium, and it is very interesting that he did have some thrombus in his right atrial appendage.

Dr. COPE: But none of that is due to the aortic stenosis or the rheumatic heart, is it?

Dr. GOODWIN: Well, only indirectly, in that I suppose the reason why they get calf vein thromboses is that they have a low cardiac output, and have been put to bed.

Dr. SHILLINGFORD: Professor Harrison, you showed the aortic valve with the calcified edges very beautifully; would you say the calcification was more on the edge rather than the base of the valve, that this was rheumatic rather than atheromatous disease?

Professor HARRISON: I can't honestly say that I am convinced that one can tell one from the other by the distribution of the calcium.

Dr. COPE: Whilst on that, one shouldn't forget that he was treated for syphilis in early life. I suppose that is quite happily out of the picture?

Professor HARRISON: I think the spirochaete left no mark on the aorta.

FINAL VERDICT

Dr. GOODWIN: I am afraid I must change my views smartly about the jaundice, because I didn't realize that the terminal bilirubin was 23 mg., and therefore I would agree with Dr. Shillingford. That is very high for cardiac failure—I thought it never exceeded 7 mg.

Dr. L. LOUGHBRIDGE: I wonder whether, in the absence of Dr. Milne, I might comment on the role of the kidney in associated jaundice and renal failure. We have certainly seen that, if the serum bilirubin is for any reason already raised in a patient who develops acute oliguric renal failure—for example, from renal

tubular necrosis, as in this case—it may be further elevated by a small amount, perhaps 2 to 3 mg., as renal failure progresses. However, in this patient the renal factor can have played only a very small part in the gross elevation of serum bilirubin. I cannot explain the absence of bile from the urine.

Professor RUSSELL FRASER: Well, perhaps the major suspicion lies on something other than heart failure.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

GENERAL PRACTICE IN THE U.S.A.*

BY

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My visit to the U.S.A. and Canada lasted six weeks, and, as I had determined to spend a significant amount of the time studying the "consumer," I took every opportunity to obtain the opinion of the patients as represented by the man in the street.

First Impressions

The impression was a saddening one. Although most people had a great respect for the skill of the medical profession their general attitude was unfavourable, sometimes extremely so. This seemed to be bound up principally with their resentment at the high fees charged and the apparent wealth of most doctors. This aspect of American medicine was indeed depressing, and it is as well that it was offset by the intense pleasure I found in the study of a large variety of educational methods, postgraduate and undergraduate. Once again academic medicine provided the inspiration, although I realized that it could not function without the organization with its less attractive features.

On my second day in the U.S. I met a lady who said to me, thoughtfully, "I am about middle age and sometimes bleed too much, but I have a first-class gynaecologist. My thyroid is inclined to be a bit overactive, but I go to a very good endocrinologist who looks after it for me. I have trouble with eczema from time to time, but I know an excellent dermatologist and he keeps it under control. But, you know, I sometimes wish I had a doctor!" At the end of my six weeks' stay in America this early impression still seemed to sum up the modern trend in American medicine.

Seller's Market

The main impression of medicine in America—and it is particularly obvious in the large centres of population where, of course, a large proportion of the people live—is that it is expensive. The American medical man sets his own financial standards, and in many places the higher his fees the better the doctor he is thought to be. Sometimes he is in fact a very good doctor, but not always. Being in the position of a seller's market (because there is a chronic shortage of medical manpower in the United States) he can dictate his terms and conditions of service, and this has two important implications.

First, he can be available or not available to provide treatment to any extent he pleases. He may or may not respond to a call for medical attention. Each episode or illness stands on its own feet, and if the doctor is too busy to attend, the patient must make other arrangements. The fact that it may be difficult to do so late at night or during the week-end need not concern the doctor. I personally observed instances of general practitioners declining to respond to a genuine call, and found this a startling contrast to the British legally binding contract to provide continuous round-the-clock service personally or by properly appointed deputy. Even before the National Health Service in Britain it was commonly understood and practised by family doctors that there was a moral obligation to attend any member of any family who was regarded as being "in the practice." In the U.S. many patients do not have a family doctor and do not "belong" to any practice.

The second implication is that the American medical profession collectively is in a very strong position to resist any attempt to introduce a health service. The period of my visit to America coincided with the highly organized resistance of the American Medical Association to the Forand Bill, a harmless little measure designed to provide the minimum of medical care to old-age pensioners at State expense. Giving evidence before a House of Representatives' Committee, an eminent spokesman for the profession did not hesitate to use such gross distortions of the truth about conditions in the British National Health Service as called for a sharp rebuke in the editorial columns of the *British Medical Journal*.* The hysterical attitude prevailing among the vocal American doctors at the time reminded me of the words of Adlai Stevenson (about the Republican Party), "They had to be dragged kicking and screaming into the twentieth century."

Most Criticized Profession

The most criticized profession in America to-day is the medical profession, although in some rural areas the doctor has retained his respect and eminence. Even when the individual patient concedes that his own doctor has earned his gratitude and respect, there is often resentment at the high fees charged and the blatant commercialism of much of what passes for medical practice. I refer to the lucrative trade in routine periodic "check-ups," often occupying the time of the practising physician to the exclusion of the treatment of illness.

That the medical profession is aware of this is shown not only by the defensive attitude of many individual members but by the enormous sums of money poured out by the American Medical Association in trying to improve public relations. Doctors are urged to be extremely careful about over-billing, and in the summer of 1959 a major topic of public controversy was whether a doctor should charge for advice given over the telephone, and, if so, how much.

Further evidence of this attitude on the part of the public is shown by the alarming increase in litigation against private physicians. The rise in litigation in Great Britain is infinitesimal when put beside American

*The second of three articles on general practice in other countries, of which the first appeared in last week's *Journal*. The final article will appear next week. This is an abridgement of Dr. Fulton's report to the Trustees of the Claire Wand Fund on his visit, under the auspices of a Claire Wand scholarship, to the U.S.A. and Canada to study general practice. The full report is obtainable from the Secretary of the Claire Wand Fund, B.M.A. House, Tavistock Square, London W.C.1.

*Brit. med. J., 1959, 2, 294.

figures, of both the number of actions and the amount of damages sought. Insurance against legal action and its consequences forms a substantial part of the physician's business expenses.

In a free market, which, so far as the practice of medicine is concerned, no longer exists in Britain, the laws of supply and demand operate with relentless and ruthless efficiency, and the plain fact is, as already suggested, that in the U.S. doctors are on a seller's market. The number of doctors has not kept pace with the growth of the population, and the current figure is 130 to every 100,000 persons. The shortage of doctors is generally recognized as the product of a deliberate policy of restriction. Vance Packard, in his book *The Status Seekers*, a best seller in America in 1959, in a chapter on "professionals" in the community, produces ample evidence of the affluence of doctors, and, though his style is mordant and his attitude has an obvious bias, which can therefore be allowed for, there is no reason to believe that he has not got his facts right.

A former fellow-student of my own in Glasgow, who had worked for a short time in the National Health Service here and had kept in touch with developments in Britain since his return to the U.S., now a very successful general practitioner in New York, said with typical candour: "In Britain medicine is a service to the people; in America medicine is a business—and big business at that." We might fairly claim, I think, that medicine in Britain is still to some extent a vocation and few would be attracted to general practice by the monetary rewards held out by the National Health Service.

Political Background

The United States of America is a federation of fifty theoretically equal States, each with surprisingly differing views on what should be provided in the way of social welfare and the manner in which such provision should be made. To attempt to review the health services of the U.S. after a visit of five weeks is something not even an American would do. To generalize from particular observations is always unwise, but some generalizations appear valid.

"Socialized medicine" is anathema in the U.S., not only to the medical profession but to most governmental agencies. The federal and state governments provide medical attention for certain groups in the population and treatment of certain diseases, and often spend generously in doing so, but the help they provide is fragmentary. The best-known government-supported medical services are those of the Veterans' Administration, but merchant seamen, native Indians, and other special groups have for many years received free treatment. There are also mental and tuberculosis hospitals, generally supported by the state governments, and some local-authority services, such as maternal and child-welfare clinics, immunization centres, and so on, similar to the British pattern. All told, these services provide some medical care for over 30 million people—less than 20% of the population. It is estimated that this accounts for nearly one-quarter of the total national expenditure on health and medical care.

By contrast, the ordinary citizen in America receives no public (government) help to provide the services of a doctor or drugs. Medical fees, drugs, hospital charges, dentistry, etc., are all very expensive and increasing in cost at a rate greater than the rise in the cost of living generally. In the average hospital the patient will have to pay about £6 a day minimum, rising to about £15 a day for a private room. Drugs, laboratory services, and all medical and surgical fees are extra. They vary widely, and are often adjusted to the income of the patient, but, as a fair example, 21s. to 35s. is a common fee for a consultation. A surgeon would expect at least £50 for an appendicectomy and an obstetrician £85 for a caesarean section. It is obvious that few people can face the prospect of an illness without anxiety on the ground of medical cost alone, to say nothing of the loss of earnings, which is rarely offset by sickness insurance unless privately contracted for. Thus insurance schemes, originally to cover the cost of the stay in hospital and, since the second world war, to an increasing extent to cover the rising cost of medical fees, are a major industry in America.

Comparison with N.H.S.

I studied several types of scheme at first hand and found the comparison with our own National Health Service illuminating. My first impression was of the attractive simplicity of the National Health Service, particularly the provision of such a wide range of general medical services by family doctors in contract with executive councils and paid largely by the extremely simple method of capitation fees.

Administrators in America were genuinely amazed at the low overhead cost of executive council administration in this country. For example, I was able to tell them that a city the size of Glasgow, with an estimated population in 1958–9 of 1,078,958, had an overall budget for general medical, dental, pharmaceutical, and supplementary ophthalmic services of £4,552,627 and that the administrative cost represented 1.2% of this total—namely, 1s. 0½d. per person. To gain a true comparison, further breakdown of this figure is interesting. General medical services, including maternity fees, represented 30s., general dental services 15s. 11d., pharmaceutical services 32s. 9d., and optical services 4s. 7½d., making a total, with administration, of 84s. 4d. per person. In addition to this sum, the patients' contributions to the last three items amounted to an average of approximately 12s. per person.

By contrast, one of the most efficiently run organizations in America—namely, the Health Insurance Plan—covering over half a million persons in Greater New York, providing for consultant as well as general medical services but excluding drugs, dentistry and ophthalmic services, had an overhead administrative burden of approximately ten times the Glasgow figure. The fact that a great deal of the administration in the National Health Service is carried out voluntarily by committees comprising lay and professional members and that some of it is financed by the professions themselves undoubtedly accounts to some extent for the remarkably low administrative costs here. It must also be borne in mind that the proportion for administration quoted above in New York is the percentage of a total which is in itself very much greater than the corresponding total in this country would be, by reason of the greatly enhanced fees charged.

Pattern of Medical Practice

The foundation and growth of the College of General Practitioners in Great Britain are generally recognized to have been partly the product of and partly responsible for the renaissance in general practice which occurred during the second five years of the National Health

Service. There does not seem to be any similar correlation between the establishment of the American Academy of General Practice and the state of general practice in the U.S. The impression gained from a large number of general practitioners, particularly in the Eastern States, was that general practice as such is gradually fading out. Patients tend very often to go direct to a consultant of their choice. At times one finds it hard to blame them. Too often the only difference to the patient between, on the one hand, consulting his general practitioner and being referred to, say, a dermatologist, and, on the other hand, going direct to the dermatologist, is the cost of the general practitioner's fee for the consultation. For this the general practitioner is not entirely to blame. A climate of public opinion has grown up under which the patient with any skin condition expects to be treated by a dermatologist.

Another complaint I often heard from both patients and general practitioners is that while there are specialists galore there are few consultants. Indeed, the only people who genuinely consult with the patients any more are the family doctors, and the specialists rarely consult with the family doctor. On the contrary more and more do they see the patients without reference to their family doctor and they seldom refer them back to him. The dermatologist may send the patient to an allergist, the gynaecologist to an endocrinologist, and so on. It is common to find a patient who has been referred from one specialist to another again and again until he or she has seen a large number of doctors in different specialties without any single one of them being aware of what is going on.

In other places there seem to be hardly any specialists at all and the general practitioner is truly "general"—that is, he is prepared to tackle almost everything, at any rate of an acute nature. He is his own physician, surgeon, obstetrician, gynaecologist, the lot. Of course there are two corollaries. One is that he does nearly all his work in hospital with full ancillary services. The other is that for a second opinion on, for example, a partial gastrectomy he will, should he wish it, have the advice of a surgeon, who may, however, practise at some considerable distance away. Wealthy patients in Florida do not hesitate when they are referred for a second opinion to, say, the Lahey Clinic in Boston, 1,200 miles away.

When one hears of British general practitioners clamouring for access to hospital beds one wonders how many of them would be capable of undertaking the full range of medical and surgical services provided by some of their American counterparts. But one wonders also how many of these American general practitioners are, in fact, genuinely capable of providing the full range of these services as well as they are provided by specialists in our British hospitals.

The custom of putting up one's plate, as it used to be called in this country, or hanging out the shingle, as it is called in America, which has almost died out since the National Health Service here, is still the established way of entering any kind of medical practice in America. Buying and selling of practices seems relatively uncommon.

Single-handed

The general but not universal pattern of practice in the U.S.A. is for family doctors to operate single-handed. There is a greater likelihood of one of them going into partnership with a specialist—say, an obstetrician or internist—than there is of his forming a partnership with another general practitioner. In this way, the general practitioner may give up maternity work and have his obstetrics done by his partner. Another favourite combination is to incorporate a paediatrician into the partnership, who looks after all the children in the practice.

Exact figures of the number of general practitioners, specialists, and part-specialists in U.S. are hard to come by, but it is generally understood that since the war specialists have doubled in number and general practitioners have dropped by 20%. This has resulted to some extent in normal medical care being provided by the specialist, the paediatrician for the younger age group and the internist for adults.

A great surprise to me was the position of psychiatry. The idea of large numbers of Americans spending many hours on psychiatrists' couches is soon found to be a Hollywood myth. Psychiatry is, on the whole, neglected in America. The emphasis is on the "crazy mixed-up kid" rather than on psychosomatic medicine. As the teenage delinquent in "West Side Story" puts it, "I'm depraved on account of I'm deprived." Only one-tenth of the psychiatric sick can afford treatment; nearly all the others do without. The surgeon who charges a large fee for the removal of an appendix at least does a once-and-for-all job. Psychiatry is so different and very few can afford to pay a large fee weekly over a long period for adequate psycho-analytical or even much less fundamental psycho-therapeutic consultations.

In large cities it is common for family doctors and specialists to work in a large office block in the centre of the area, generally called the medical arts building. There is nothing homely or intimate about this, rather an atmosphere of bustle and efficiency, with the doctor directing the activities of a large and mixed ancillary staff of secretaries, nurses, and technicians. There are often private radiologists and laboratory services, and the inevitable pharmacy on the ground floor.

Profit Motive

In the best of these establishments the medical skill in diagnosis and treatment is superb. The primary motive remains financial profit. There may be nothing wrong in this; certainly neither the patients nor the doctors seem to feel anything wrong in it, but it is very far removed from the traditional British concept of a family doctor in his own practice.

There is a definite trend away from home visits. Before the war the proportion was not much different from our own in Britain; now less than one in twelve consultations takes place in the patient's own home and invariably costs more—as much as twice the office consultation. Generally speaking, if a patient is ill enough to be confined to bed he is admitted to hospital for medical care.

The original pattern of medical care of ill people in hospital rather than their own homes has been accentuated by the growth of insurance schemes. For example, Blue Cross pays only for investigations carried out in hospital, so patients want to go into hospital even although they are not, as we would consider, hospital cases. It may be that the growth of insurance schemes to pay for doctors' services will in time reverse this trend.

It is undoubtedly a fact that the American doctor, both specialist and general practitioner, is in a position to make money out of illness by virtue of a method of payment which produces the frame of mind and the attitude towards his work which I found to be so prevalent.

Hospitals

The American hospital is primarily a workshop in which doctors, as private independent agents, carry out their activities. Apart from the houseman and the resident staff, voluntary hospitals do not employ doctors, with few exceptions, and these generally in hospitals with a teaching association. What is more unusual to a British observer is the fact that there are relatively few trained nurses, although the average voluntary general hospital employs two or three persons for every patient. The highly paid registered nurse now works a five-day forty-hour week largely on administrative and supervisory duties. Nursing as it is known in Britain, or bed-side care as it is called in America, is carried out by "practical nurses" with a one-year training or by "nursing aides." They earn less than half the pay of a trained nurse. Student nurses are students and often take a university degree at the same time. They pay for their training both in hospital and at the university.

Not only, therefore, does the average American patient have his own doctor to look after him in hospital but, if he can afford it, he has his own nurse or nursing team at a cost of $18 each or $50 a day. The less affluent patient often has to rely on his visitors to provide some of the tender loving care which the British medical profession acknowledges is so often rendered by hospital nurses and is responsible, or partly responsible, for the patient's recovery.

Description of an Intermediate Type

Voluntary hospitals range from the large teaching hospitals down to the small community hospitals. A description of one hospital I was able to study in detail may give a better idea of the organization than a summary of the overall position.

The Lawrence and Memorial Hospital, New London, Connecticut, is an "intermediate" type of hospital serving a community based on New London and Groton on the Thames River, with a combined population of 100,000 people and, in addition, a scattered farming community in a semicircle of radius 15 miles.

There are 220 beds (the new hospital will have 310) on two floors. Of these, 40 are for maternity—that is, lying-in beds. The antenatal beds do not exist as a separate unit, but these women are accommodated in the ordinary female wards, either medical or surgical according to the type of case. When the new extension is completed medical and surgical beds will be in separate wings.

The junior medical staff in the employment of the hospital is made up of four interns (when I visited the hospital only one of these posts was filled) and ten residents, four in surgery, three in medicine, and three in obstetrics and gynaecology. It is an accredited hospital—that is, recognized for training residents as future specialists. In some hospitals an experiment is being carried out in training future general practitioners in suitable residencies.

The "attending" staff, who receive no remuneration from the hospital, supervise the teaching programme of the interns (they are all rotating internships) and the residents under the control of an education committee.

Each specialty, medicine, surgery, etc., has an elected or appointed head of the department who is legally and morally responsible for the care of all patients in his department, either private patients of his own or other "attending" or "courtesy" staff, or "hospital" patients who cannot afford their own doctor and who are looked after by the residents or interns.

The "attending" staff, numbering about 60, look after their own private cases and are also responsible for "staff" or "service" patients under the overall leadership of the head of the department.

"Courtesy" staff, numbering about 40, look after their own private patients only and have no other clinical responsibility in the hospital, but are required to attend the regular staff meetings and take part in the educational programme. They are mainly the general practitioners of the neighbourhood who have not (yet) gone on to specialize. There has been a steady progression towards specialization, and it is expected that ultimately only those who have passed the Board examination in a specialty will be allowed to treat patients in the hospital, though there is a move towards a department of general practice for general practitioners' cases only.

This department of general practice is quite different from the departments of general practice found in many hospitals of this size and even in the larger teaching hospitals (but more in Canada than in the U.S.) at the present time which exist as part of the organization of the hospital. Such a department ranks as equal with the other departments of medicine, surgery, etc., except that it has no patients. It has an equal say in the running of the hospital, the arrangements for accreditation, administration, education, and "screening" of doctors who wish to work in the hospital at various levels. It must be emphasized that to prevent a general practitioner from looking after his own patients in hospital is tantamount to depriving him of his livelihood, since nearly all ill people are cared for and treated in hospital and not in their own homes.

If a patient wishes to have her baby in hospital she may engage her own doctor to attend her and make her own arrangements with him. If she goes in as a ward case he is not allowed to continue to look after her should any one or more of a standard list of complications develop. In this event he must call a specialist. He may call the "service" specialist free, but if he wishes the specialist of his choice the patient must pay.

Paying the Bill

In fact, nearly all women who can afford it engage a specialist obstetrician for their confinement. They attend his private rooms or office for antenatal care and go into the hospital for the delivery. The hospital has no financial dealings with the doctor in this case, since the patient pays him direct, an average fee in this town being $200. The rule is for a very short stay after the confinement, not only on clinical grounds but for reasons of cost. The hospital will charge another $250 to $300 for a week's stay for a confinement, of which something in the region of $100 is likely to be met by Blue Cross, to which the woman's husband usually contributes.

The above figures were obtained from the Connecticut State Medical Society and the administrative officer of

the hospital, and were verified from a perusal of a number of actual accounts. Another example is a hospital bill for $104 for tonsillectomy in a child, aged 4, who was in semi-private accommodation for two days. (This included "anesthesia," by which is implied the administration of an anaesthetic by a nurse anaesthetist. A specialist who gives anaesthetics is an "anesthesiologist.") In this case Blue Cross covered all costs except the difference between the hospital charge per day ($18) and the standard credit per day ($12), so the parents had only to pay $12 of the hospital bill. They had also, of course, to meet the surgeon's bill.

The existing pattern of health insurance is typically American in being a complex mingling of a host of non-profit schemes with private enterprise operations of a standard commercial type.

In the first category come the 90 Blue Cross and 70 Blue Shield plans serving different parts of the country, all financially independent and each determining its own rates and benefits. Both are non-profit-making and have been in existence for over 20 years. Blue Cross, which caters for hospital costs, made rapid strides right from the beginning, whereas Blue Shield, which helps to pay the doctors' bills, expanded mainly after the second world war.

In the other category are the various insurance companies which, unlike Blue Cross and Blue Shield, are not exempt from tax. Nevertheless, they now cater for rather more people than their earlier rivals.

Group Health Incorporated

One of the earliest experiments in the U.S.A. in prepaid medical care began in Washington, D.C., and is known as Group Health Incorporated. It is a co-operative which groups of people may join by agreeing to pay an annual subscription graded from time to time, according to the cover provided for the individual or the family, and receiving in return general and specialist care (up to stated limits) which are provided almost exclusively by physicians employed by the organization on a full-time salaried basis. The premises from which the doctors practise are owned by the organization and there are facilities for straightforward investigations. The scheme is administered voluntarily by a lay board of trustees advised by a medical director.

The general standard of performance is high, and most of the doctors who have joined the staff are those who believe that they can in this way practise medicine more honestly than having to resort to the commercial methods which would nevertheless enable them to earn more money. The scheme has functioned for many years and I was unable to find any evidence that it had been copied. Washington, D.C., is a unique city, and it may be that a group of people similarly minded cannot be readily found to institute a similar scheme elsewhere in America.

Industrial Medicine

There are very wide variations in the provision of industrial medicine in the U.S. Most large establishments have a first-class organization providing continual industrial medical care including hygiene, periodic checks on employees, elimination of medical hazards, and treatment of injuries. In the provision of medical care of sick persons the situation is not so clear. Conflict between the doctor engaged in industrial health, frequently called the "plant doctor," and the private physician is even more pronounced than in Great Britain, and attempts have been made by the American Medical Association to define more clearly their spheres of influence and to bridge the gap. There is now a recognized code of ethics that is by no means always kept by the various parties.

Industrial medicine is much more likely to shade imperceptibly into medical care in the U.S. Many large concerns try to attract workers by the provision of fringe benefits, including an attractive insurance scheme for medical care of the worker and his family. Others more altruistically minded have found that the lack of medical care of sick employees has created a situation which they have tried to correct by setting up their own medical care schemes. These vary from small private ventures to the well-known Kaiser Permanente scheme, in which the buildings from which the doctors practise and even the hospitals where the patients are treated are owned by the organization, which employs its own staff exclusively to provide these services.

Another reason for the direct provision of medical care by industrial concerns is that when initially the medical care was contracted out to private physicians, the cost to be covered by an insurance scheme, there was evidence of increasing abuse both by patients and doctors, and the concerns claimed that they found it cheaper to run their own schemes. Sometimes, however, these were not welcomed by employees, to many of whom the provision of medical service by a private physician was regarded as a status symbol.

Another type of organization is that created by trade unions or a group of trade unions for their members Probably the best known of these is the United Mineworkers' Union scheme, and to some extent their history follows the pattern already described by the development through contracts with private physicians to the setting-up of their own organizations for the reasons given.

In nearly all these cases, to make the scheme acceptable to the patients and to counter criticism from the organized medical profession, a deliberately high standard of medical care is aimed at and usually achieved.

Industrial Medical Centre

As well as having discussions with officials of the U.S. Department of Health, Education, and Welfare concerned with industrial medicine and a number of doctors engaged in this form of medical practice in different places, I had the privilege of paying a visit to the medical centre of a large and famous boat-building establishment carrying on a great deal of secret work in the field of propulsion by nuclear energy. I was very much impressed by the medical centre, its organization, and staff.

This is provided on a lavish scale by the management as part of the normal running expenses of the yard, which employs about 11,000 workers. Without technical knowledge in this highly specialized field I cannot say whether the precautions taken against contamination are adequate, but I could see the very elaborate arrangements made to check workers in varying degrees of contact with radioactive materials. A large laboratory, fully equipped and staffed by competent technicians, is permanently engaged in specialized investigations, and eminent authorities to whom I later spoke confirmed my own impression of the excellence of the organization. I feel more competent to assess the arrangements for

dealing with accidents, and, in fact, witnessed the first-aid team going into effective action during my visit when a staging collapsed and caused serious injuries to two men. The medical centre is equipped with *x*-ray apparatus and other facilities for immediate treatment and proper assessment by the medical staff before removal of the injured person to hospital.

I was more surprised with the extent to which the organization concerned deals with rehabilitation. It employs a number of full-time physiotherapists as well as nursing and technical staff, and contracts with an orthopaedic surgeon to provide such services as are required to supervise treatment. In an establishment of this kind it may be difficult to re-employ a seriously handicapped worker, but the management seems to assume a moral responsibility in these cases, and I saw a number of employees who had been receiving remedial exercises many months after their return to some kind of work in the yard. The provision by purely private enterprise in this way of what would be regarded as general welfare services in Great Britain is a typical feature of America and must inevitably produce a very wide variation in the provision of what has come to be regarded as the right of every injured or disabled person in this country.

I have described what is probably one of the best examples of industrial medicine, including casualty service and rehabilitation, in the U.S. to show how well it can be done when the will is present. There are many other examples of first-class schemes. Whether or not rehabilitation should be left to industry (and perhaps therefore done most inadequately, if at all) or should be carried out as a nationally financed scheme, as it tends to be in Great Britain, is more a political question than a medical one.

Socialized Medicine

Responsible officials expressed the view that in many American States the trend in the medical societies and associations is towards an attempt at compromise with the social forces in the community, though they are being hampered by a considerable minority of vociferous diehards who blindly resist all forms of control. On the whole, the state medical societies prefer to yield in an organized way, maintaining a semblance of solidarity and internal discipline. "Socialized medicine" is not the real threat, since it is extremely unlikely that any American government would go so far as to try to introduce anything that could be called by that name. There are, however, powerful forces in government circles and in organized labour who wish to introduce some form of insurance against sickness, and the principal threat to the doctors is the understandable desire to be able to predict with some degree of accuracy the cost of such a scheme. This would appear to involve determining the fees for various items of service. Even when the patient pays a considerable proportion of the doctor's fees, the insurance company is still left with an unknown quantity and cannot be expected, in the words of one insurance official, "to cover the blue sky above."

Postgraduate Education for the Family Doctor

"The continuing professional education of practising physicians constitutes one of the most important, difficult, and neglected problems facing Americans to-day."

So said Dr. Lawrence B. Ellis, Boston, in a specially contributed article, published by the *New England Journal of Medicine* in 1954, on the work of the New England Postgraduate Medical Institute, of which Dr. Ellis was the president. The weakest link in the chain between producer and ultimate consumer is the degree to which the family doctor is out of date. Millions of dollars are poured out by various foundations in research; wonderful new discoveries are continually being made in laboratories; but there is a widespread neglect to ensure the fruits of this knowledge by maintaining the practising doctor at the peak of efficiency in the proper techniques of its application. Nor have medical schools in the U.S.A. met the need, being reluctant to venture into a field that might lead to a further drain on their overburdened exchequers. The gap is particularly wide in the case of rural doctors who are isolated from their fellows and whose practices often embrace of necessity specialties with which their urban colleagues need not concern themselves.

For the most part general practitioners have had to take the initiative themselves in organizing postgraduate or continuing education suitable for family doctors. In this field the American Academy of General Practice has done a great deal. Criteria for continuing membership are strict and rigidly enforced. A minimum amount, currently 150 hours, of duly authenticated postgraduate study must be carried out each three-year period. As facilities for this were often lacking for many of their members throughout the U.S. the Academy moved into this field. Sometimes it works with the established authorities in hospitals and medical schools, as the College of General Practitioners in this country has always done, but often the Academy organizes and carries through a very ambitious programme entirely under its own auspices. This may be combined with a social or holiday occasion. For example, a fortnight's cruise in the Caribbean is combined with a not-too-intensive refresher course ranking as one week's postgraduate instruction. The American general practitioner has to pay his fees and out-of-pocket expenses for himself, but this ranks as a business expense.

Like the B.M.A., the American Medical Association and the state medical societies organize meetings of a clinical nature, and, of course, the medical schools run some courses. Many, however, as I found at Harvard University in Boston, are more concerned with specialist training, and the main authorities responsible for the organization of postgraduate education for the general practitioner around Boston are not the medical schools. The arrangements there are fairly typical and worth fuller description.

New England Postgraduate Medical Institute

Postgraduate education is mainly co-ordinated by the Massachusetts Medical Society, which since 1952 has sponsored the New England Postgraduate Medical Institute, which acts as a clearing-house, a central agency or source of all information relating to post-graduate medical education in Massachusetts and New England. A brochure of each month's coming events, "What Goes On," is sent free to 18,000 doctors in New England, and a complete index of all activities is kept permanently up to date.

The role of the P.M.I. is by no means passive. The relative failure of existing courses to attract new general practitioners to attend forced the young P.M.I. to organize its own courses, which were an immediate success, with a total of 221 doctors enrolled for the first

general course at an average cost of $1.50 per hour. Intensive courses of one or two weeks are now held in ten different areas up to 165 miles from the headquarters in Boston.

More recently, successful extended courses have been organized by the P.M.I. in centres throughout the area, held usually in the local community hospital once every week or every two weeks, consisting of 10–12 sessions of 2–3 hours each. An eminent visiting speaker gives the lecture at these courses, usually using local clinical material for demonstration. The attempt is to develop in the local hospital an approximation to the teaching hospital. These courses are only organized on the direct request of and in co-operation with the local representative committee or society, but are otherwise managed by the P.M.I., which in the earlier years hand-tailored every programme but is now gradually standardizing the work. The attempt is to cover the necessary field in a four-year period.

Some of the subjects studied seem to us very specialized. For example, cardiology is a favourite topic for intensive study. But when it is remembered that many of these general practitioners own and operate their own electrocardiograph machine, read their own tracings, and manage most of their own serious cardiac cases, including the administration and control of anticoagulant therapy, the need for a deep knowledge of the subject is apparent. Similarly, doctors may need to have considerable surgical experience and be kept up to date in the best methods of carrying out practical surgical procedures.

Continual research is carried out by the P.M.I. on methods of improving postgraduate education, including a typically thorough "consumer research," to assess the reactions of the participating doctors and their assessment of the value of the courses. Each speaker is subsequently informed of the results and "instructed" by the P.M.I. on how to improve his technique.

The P.M.I. now collaborates with Albany Medical College, which has pioneered this kind of work, in organizing two-way F.M. radio conferences. For several years Albany sponsored these through a network of 20 hospitals located north and south of the university along the Hudson River Valley in New York State. Now a new station has been built in north-western Massachusetts and the studio is in the P.M.I. headquarters in Boston. Each participating hospital has its own transmitter and receiver. The idea is a two-way link between the teaching centre and the peripheral community hospital and its staff, which includes, in effect, all practising doctors in the area. It is supplementary to the normal postgraduate methods rather than a substitute for them.

The actual courses, taking one with another, are paid for in full by the attending doctors, but the other activities of the institute are financed by grants. The Massachusetts Medical Society, the largest contributor, pays one-sixth of the expenses, totalling $45,000 per annum, and a large number of other public and private health organizations and research foundations the remainder.

As in the U.K. there is the tendency for the good or better-than-average doctor to make the necessary sacrifice of money and time to attend these courses. Often those who need the instruction most are more laggard and have to be prodded. It is hoped that patterns of behaviour that are set up will be catching, and public opinion, often judiciously primed by propaganda, is making the patients more demanding and more knowledgeable.

Future of the Family Doctor

The precarious position of the family doctor in America is giving concern to many serious thinkers in the medical profession there. The dilemma may be stated as follows: The human aspects of medicine instinctively bring to mind the idea of an individual practitioner, the family doctor. The advanced technical and scientific aspects of modern medical practice are associated in our thoughts with the institution. The very name implies a big, complex, depersonalized organization, just as the name family doctor conjures up a mental picture of a friendly medical counsellor and guide.

Can the family doctor be brought within the ambit of the advanced medical centre and still remain a family doctor? Considerations of time and distance are the immediate objections, but even in Britain probably two-thirds of the people live in what might be called urban or metropolitan areas, and it is expected that within another generation 75% of all Americans will be so situated. Their medical attendants, therefore, will be within striking distance of a fairly large medical centre, in many cases associated with a medical school. They will, of course, have many more community hospitals on their doorstep.

One possibility is, therefore, that the family doctor will be a good general physician "attached" to the medical centre, seeing there those of his patients who need more intensive investigation but carrying out the major part of his normal practice in his usual consulting-rooms. Full facilities for diagnostic investigations and the advice of various specialists would be available in the centre, but the traffic would not be all one way. The family doctor as a full member of the team would contribute to the work of the centre in all its aspects of patient care and education, both undergraduate and postgraduate, and in medical research. Those doctors whose practices were in the surrounding suburban communities would form the ideal link between the medical centre and the area it served. This can be seen as an opportunity to develop a metropolitan programme of advanced medical diagnosis and care.

For the family doctor the advantages would be in enhanced status and greater satisfaction and interest in his work. Postgraduate education that is a part of one's daily work is in the final analysis the most efficient and satisfactory. It is what makes the full-time clinical teacher what he is, but, unlike him, the family doctor could not lose touch with the realities of life and work outside the centre.

The influence of such a system on the teaching of undergraduates would be immense. There is an artificiality about the introduction of the family doctor on rare occasions into the teaching course and of the student for short periods to the practice of the family doctor that would be totally absent from a system based on complete integration of the day-to-day work of the family doctor with the higher-level activity of a medical centre for diagnosis, therapy, research, and teaching.

This concept, though advocated with vigour by some far-seeing Americans, is little more than a pipe-dream at present, whereas the family doctor centre, run in conjunction with the General Practice Teaching Unit of Edinburgh University in the same building but as a

separate entity, began operating along very similar lines in June, 1959, and is now open to all doctors in Edinburgh and the surrounding districts.

Conclusion

The visit was too short, but the fact that I was able to find out so much in such a short time was owing partly to the attractive quality possessed by most Americans of showing not the slightest resentment at questions of a most searching nature from someone who is obviously showing a genuine interest in their way of life and method of work. Americans seem to be able to combine a faculty for critical self-assessment with something approaching worship of the American way of life. I was prepared to accept the fact that in the organization of medicine our way was different from their way without always trying to make comparisons. They seemed to find it difficult to accept that, in different circumstances, different methods of solving the same problem might both be correct. Although many of them as individuals tried hard to avoid it, their general attitude was that their way of doing something was the right way. This criticism applies mainly to their attitude towards the organization of medicine. With regard to the clinical and academic aspects they showed a greater willingness to accept change, to experiment, and to learn from others than is usually found among people in corresponding positions in this country.

Acknowledgments

I am deeply grateful to the trustees of the Claire Wand Fund for giving me the opportunity to pay a visit to the New World at a time when the medical services there were in such a state of flux and when I myself was trying to think seriously about the pattern of medical services to be desired in this country.

CEREBROVASCULAR ATTACKS

[FROM A SPECIAL CORRESPONDENT]

A conference on occlusive cerebrovascular disease, the third of its kind, was held at Princeton, New Jersey, on January 4, 5, and 6. The conference was sponsored by the American Neurological Association and the American Heart Association. Sixty participants, mostly from centres in the United States but with a few from England and Scandinavia, enjoyed an excellently organized, stimulating, but perhaps rather over-full programme, under the chairmanship of Dr. CLARK H. MILLIKAN.

Incipient Strokes

Three aspects of occlusive vascular disease of the brain were discussed: incipient or impending strokes, progressive stroke, and completed stroke. More than half the time was given to the first of these, and a rather wider field than the title was covered. It included all transient attacks and manifestations of focal intermittent insufficiency caused by occlusive disease of the arteries of the head and neck. Dr. R. G. SIEKERT (Rochester, Minn.) pointed out that the diagnosis of these ischaemic attacks was mainly clinical and that differentiation from migraine and Ménière's syndrome could be difficult, as well as from other causes of syncope. He felt that these attacks were usually transient deficits of neurological function without any suggestion of a discharging lesion, lasted 15 to 30 minutes, usually conformed to the same pattern, and produced symptoms such as vertigo, nausea, weakness and numbness in any or every limb, diplegia, hemianopia, and dysphasia. When the circulation of the hind brain was involved, turning the neck or wearing a tight collar might produce both symptoms and a slow-wave focus (usually focal) in the E.E.G. Many cases went on to infarction, he said, but later speakers thought that it was surprising how benign this condition might be. On pathogenesis, Dr. J. P. WHISNANT (Rochester, Minn.) pointed out that, although atherosclerosis of the cervical carotid and vertebral arteries with stenosis was the commonest finding in these attacks, this often occurred without symptoms, and he adduced post-mortem evidence for this view. In his symptomatic group he thought the carotid stenosis more important than the vertebral. Professor D. DENNY-BROWN (Boston) thought that fibrin-platelet embolism from atherosclerotic stenosis of large vessels, combined perhaps with hypotensive states and possibly higher blood viscosity, was the main cause. Except in acute hypertension he thought vasospasm played no part. The factors leading from transient phenomena to irreversibility were concerned with the efficient pressure and flow of collateral circulations controlling oxygenation and oxidation of the brain, and eventual irreversibility was produced by local haemoconcentration.

Special Investigations

Ophthalmoscopic studies were described by Dr. R. W. HOLLENHORST (Rochester, Minn.) and Dr. ALBERT HEYMAN (North Carolina), the former finding studies of retinal pressure useful and the latter showing delay in the arm-to-retina circulation by intravenous injection of fluorescein with some beautiful pictures of the retinal circulation. It was thought that this type of investigation was equal in value to ophthalmodynamometry, although it was difficult at times to correlate the two.

The investigation of patients with suspected cerebrovascular disease was fully discussed and applied equally to the transient, progressive, and completed lesions. Professor G. NYLIN (Stockholm) described his study of the dilution curves of radioactively labelled erythrocytes with phosphorus-32, and Professor PERITZ SCHEINBERG (Miami) described the considerable advances made in measuring the cerebral blood-flow. General observations on total flow could most accurately be made by using the gas crypton-79, and directional, qualitative blood-flow could be estimated for almost any area of the brain by the use of iodine-131 antipyrene. This had been found the most useful for measuring changes of flow in focal and transient ischaemic attacks. Dr. S. S. KETY (Bethesda, Md.) showed that in differential carotid and jugular-bulb studies there was preferential retention of flow, two-thirds to one-third on the ipsilateral side, and he thought this was more often due to anatomical distribution of the venous drainage than to cerebrovascular disease.

Arteriography was a controversial subject, and many stressed the potential and recorded dangers of this procedure, but some new, interesting, and less harmful techniques were described. H. L. BAKER (Rochester, Minn.) found that the double-barrel technique of intravenous aortography was excellent for the aortic arch, but this did not show the carotid bifurcation clearly.

Dynamics and Anticoagulant Treatment

The dynamics of thrombosis were discussed by Professor SOL SHERRY (St. Louis), who described the changes in thrombolytic activity associated with disease, electric convulsion therapy, pyrogen-injections, and ischaemia. Unfortunately there was no information on changes of thrombolytic activity in cerebrovascular disease, although this was known to be decreased in diseases affecting the pia mater and after pneumoencephalography. Dr. J. P. WHISNANT showed that atherosclerosis was more prevalent in the larger arteries and that multiple lesions were common. Professor R. D. ADAMS (Boston) showed how common was spread by embolism and that by propagation of thrombi, and thought the emphasis on diseases of extracranial arteries was justified. Dr. E. C. HUTCHINSON (Stoke-on-Trent, Staffs) had also found in 100 necropsies how common was multiple

occlusion, particularly in the vertebral arteries, and illustrated this with some impressive pictures.

Dr. A. BARHAM CARTER (Ashford, Middlesex) showed in a controlled clinical trial that the immediate results in patients with worsening strokes could be significantly improved by anticoagulants, particularly if treatment was begun early, and thought that phenindione was a safer oral anticoagulant than coumarin. Professor J. S. MEYER (Detroit) said the use of fibrinolysins might become more widespread once they had been tested for effectiveness and toxicity, but thought that their marketing had been premature. In completed strokes there was contradictory evidence on both their dangers and their beneficial effects. From New York Professor IRVING S. WRIGHT, Dr. ELLEN MCDEVITT, and Dr. S. N. GROCH thought that long-term anticoagulant therapy was justified and in a controlled series showed effective protection from recurrence of cerebral infarction, from pulmonary embolism, and from myocardial infarction, with only 16% of haemorrhagic complications and no increase in death rate attributable to treatment. On the other hand, Dr. ROBERT BAKER (Los Angeles) in a similar, well-controlled series found no protection from further cerebral infarction, protection from recurrent transient ischaemic attacks, and an increase in death rate from cerebral haemorrhage in the treated group.

Surgery

The surgical results of treatment were very impressive, but it was agreed that the surgeon's material was highly selective and therefore not comparable with that of the physician. Dr. MICHAEL DEBAKEY and Dr. E. STANLEY CRAWFORD (Houston, Texas) pointed out the difficulty of selecting patients for surgery as the multiplicity of lesions commonly found made for uncertainty as to which particular occlusive phenomenon was the cause of the patient's symptoms. They thought that a 50% reduction in the diameter of the internal carotid artery was necessary before symptoms occurred; and if a single stenotic carotid lesion was shown angiographically and ischaemic symptoms were present, then this case was ideal for surgery. Age was no contraindication in itself, but a short expectation of life from widespread atherosclerosis was. If the occlusion was complete most speakers thought operation contraindicated, but Dr. DEBAKEY showed some good results with bypass graft operations even in this event. This Houston school showed some remarkable results in progressing strokes. In 27 patients, of whom 22 had internal carotid occlusions and 5 vertebral, 17 were asymptomatic in a follow-up of six months to four years and no deaths were attributable to operation. A film of the technique of operation was shown, and after removal of the atherosclerotic plaque and occluding thrombus a patch graft was used to prevent residual stenosis. Professor C. ROB (Rochester, N.Y.) did not think this patch was often necessary, and in a personal series found that after 2½ years 15% of his patients had a subsequent stroke.

Main Stumbling-block

The final impression was that the multiplicity of atherosclerotic lesions in the extracranial portions of the arteries supplying the brain is one of the greatest stumbling-blocks in diagnosis and treatment. If diagnosis is to be exact and surgery to be of any use, arteriography is essential, though not without danger. This investigation may be made efficiently by different techniques, but should be done by experts with surgeons at hand experienced in vascular work. Anticoagulant therapy is of use in selected cases, but indications and contraindications need further definition.

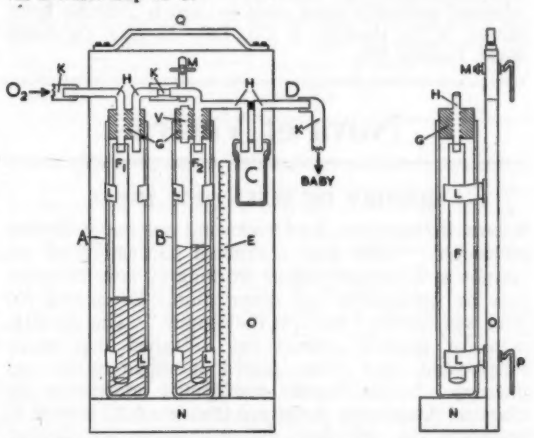
The conference closed with some well-chosen and thoughtful words from one of the most distinguished participants, Professor H. G. WOLFF (New York), who thought that workers in this field should realize they are still in an experimental stage with need of clearer understanding of terminology, of less harmful methods of investigation, and of more easily controlled therapy.

New Appliances

SIMPLE WOULFE BOTTLE AND SAFETY-VALVE UNIT FOR USE IN NEONATAL RESUSCITATION

Dr. C. G. H. NEWMAN,* paediatric registrar, the Whittington Hospital, London N.19, writes: New safety measures may never be used when their virtues are offset by disadvantages such as bulk, clumsiness in use, or expense. It is generally accepted that when administering oxygen intratracheally to newborn infants there may be some risk of applying too high pressures, particularly when the administrator is relatively inexperienced. This risk can be avoided by the use of a safety valve. Such valves are incorporated in resuscitation trolleys, but are often omitted when no such specialized and expensive equipment is available. A simple and inexpensive unit incorporating such a safety valve has been built at the Whittington Hospital from materials freely available in hospital workshops, and it is suggested that some such device might find a place in labour wards and elsewhere where intratracheal oxygen may have to be administered to neonates.

The basic plan is as follows (see Fig.). Oxygen flows from the cylinder through the equivalent of a Woulfe bottle (A)—in fact, a catheter-sterilizing tube, with rubber bung and metal and plastic tubing arranged as shown. The principle of this humidifier is conventional. The humidified gas then flows through the metal tubing to the outlet at D, via a water-trap at C.



Drawing (not to scale) showing general plan and components. A, Woulfe's bottle. B, Safety-valve bottle. C, Water-trap. D, Outlet. E, Pressure scale. F. Plastic tubing: 3/16 in. (4.7 mm.) diameter, 16 in. (40.6 cm.) long. G, Rubber bung, perforated as shown. H, Brass or stainless-steel tubing. K, Rubber tubing. L, Terry clip. M, Adjustable mounting-clip for oxygen carrier and slot. N, Base block. O, Base plate. P, Mounting-clip (fixed). Q, Carrying-handle. V, Gas escape vent.

A safety valve is inserted into the side of the metal tubing just before the water-trap. It is a simple hydrostatic valve, made by modifying a second Woulfe bottle tube (B). The only difference between A and B is their connexions. B has a vent (V) through the rubber bung free to the atmosphere, and the long inner tube is connected into the side of the tube carrying gas to the baby. Gas can bubble out down the inner tube (F_2) and up again to escape through the vent (V) whenever its pressure exceeds the hydrostatic pressure preventing its escape. (In fact, the height of water above the lower open end of F_2.) The height of water in B determines the "blow off" pressure of the safety valve. The actual pressures measured at the outlet D in centimetres

*Now at the Children's Hospital, Ladywood Road, Edgbaston, Birmingham 16.

of water at different levels in B were found to be about 5 cm. higher than the actual level in centimetres. This is presumably due to factors such as friction and viscosity, and might well vary slightly between different units.

It is therefore possible to limit the pressure at which gas can be delivered at D by adjusting the water level in the safety valve B. This is done by varying the water level in tube B by removing the rubber bung and either pouring water out or adding to it. Should pressure tend to rise either from back pressure from the infant's lungs or because of increased flow rate from the cylinder, gas will exceed the hydrostatic pressure in the valve and will escape. This will prevent potentially harmful rises of pressure in the patient's air passages.

The unit is virtually unbreakable. The components are easy to clean and to sterilize, and, as it is unnecessary to remove the metal tubing from the rubber bungs, assembly is easy and relatively proof against error.

The following is a list of the components as assembled in the hospital workshop: 2 plastic catheter sterilizing tubes, complete with rubber bungs. 2 lengths (15½ in.; 39 cm.) of plastic tubing, external diameter 3/16 in. (4.7 mm.). Brass and rubber tubing, as illustrated. Flattened brass strip for carrying-handle and clips for attaching to oxygen-cylinder carrier. Nut and bolt for adjustable clip. 4 Terry clips for holding catheter-sterilizing tubes. Base plate, 6 by 21 in. (15 by 53 cm.), with footpiece.

It would be preferable to use plated tubing instead of brass. The materials are inexpensive. (Registered design pending.)

I thank Mr. H. Kourik and his staff for their helpful suggestions and for manufacturing the prototype. A perfected version is being made by, and is available from, Messrs. A. L. Hawkins & Co. Ltd., 15 New Cavendish Street, London W.1.

Nova et Vetera

HISTORY OF SCIENTIFIC IDEAS

Science derives from the Greeks and was one with their philosophy. They had a rational conception of the cosmos as an orderly whole working by laws discoverable by speculation and observation. So science for long was termed "Natural Philosophy." The development of modern science has disturbed this happy relationship, and Osler feared it might prove her undoing. In his famous presidential address to the Classical Association at Oxford (*Brit. med. J.*, 1919, **2**, 1) he said:

"Specialism, now a necessity, has fragmented the specialties themselves in a way that makes the outlook hazardous. The workers lose all sense of proportion in a maze of minutiae. Everywhere men are in small coteries intensely absorbed in subjects of deep interest, but of very limited scope."

With the aim of uniting once more philosophy and science, Professor Gillespie, who holds the chair of the history of science at Princeton University, has written this learned and debatable book,* which traces the development of scientific philosophy by means of the history of science from Galileo to Einstein. The medical reader will find that due weight is given to the lore of Paracelsus, to Harvey's great discovery, and to the insight of John Locke and of T. H. Huxley. In regard to other medical pioneers the author is strangely reticent. There is but brief reference to the vision of Pasteur and the work of Robert Koch and Virchow, while nothing is said of the knowledge revealed by Lister, Ferrier, Horsley, Sherrington, and others, or of the latter-day triumphs of physiology, pathology, and biochemistry, which surely all contribute to the modern concept of a philosophy of science. To atone for this reticence the contributions of the physicists, chemists, geologists, biologists, astronomers, and mathematicians are traced with sedulous care and often with biographical detail. Lamarck, Cuvier, Darwin, Lyell, and Mendel receive their just meed of praise, while the influence of the work of Lavoisier, Goethe, Diderot, and others is perhaps somewhat overemphasized. But Professor Gillespie's hero is James Clerk Maxwell, the prince of nineteenth-century physicists, "whose unification of light and electro-magnetism in field theory worked the aether right into the bone and texture of classical physics."

This book shows that scientific philosophy is yet in the making. Even though in the light of modern discovery some of the gathered pebbles are beginning to assume a definite pattern, the scientists and philosophers still gaze upon an unknown and illimitable ocean.

ARTHUR S. MACNALTY

**The Edge of Objectivity. An Essay in the History of Scientific Ideas.* By Charles Coulston Gillespie. (Pp. 562+vii; illustrated. 42s.) Princeton, N.J.: Princeton University Press. London: Oxford University Press. 1960.

PARÉ'S CASE REPORTS

The passages selected from the writings of Ambroise Paré which are offered in this volume* have been available in English since 1634, when Thomas Johnson's translation was first published. This folio volume is now expensive, and, as Dr. Hamby writes in his introduction: "Charming as it is, Johnson's Elizabethan English gives the modern reader a little distorted flavour to the old Frenchman and his work. He has even become considered 'quaint,' I fear, in the same use of the term reserved for antimacassars and bogus antiques of other sorts. The word applied to Paré is as insulting as it would be in the case of George Washington or Benjamin Franklin."

It is true that case reports have a perennial interest for any doctor. These laconic and straightforward accounts, lifted from the exposition and discussion of outmoded ideas in which they are embedded in Paré's original text, reveal the man and the medical practice of his time in an unequivocal fashion. That the sixteenth century was a turbulent period for France is a historical fact, but the general attitude to cruelty and violence at that time is brought home to us when we find it unconsciously reflected by one who has always been considered the most humane of surgeons. He tells us how a beggar had obtained alms by feigning leprosy and was condemned to be whipped through the streets on three successive Sundays. On the third Sunday, "excited by the cries of the people, the executioner worked so with his lash that he [the beggar] died a little later . . . which was no great loss to the country." Another malingerer, a woman, was kicked and beaten by the doctor examining her; but fortunately the remaining accounts show us the doctor in his customary role of one who treats the effects of violence rather than one who inflicts it. Gunshot and sword wounds were common enough and are well represented here, but the case of the child crushed by a coach wheel must be one of the earliest

**The Case Reports and Autopsy Records of Ambroise Paré.* Compiled and edited by Wallace Hamby, M.D., F.A.C.S. Translated from J. P. Malgaigne's *Œuvres Complètes d'Ambroise Paré.* Paris, 1840. (Pp. 214+xx. 52s.) Springfield, Illinois: Charles C. Thomas. 1960.

in the long record of traffic accidents. Among the records of other cases may be found cancer of the breast and the lip, aneurysm, plague, malaria, syphilis, and smallpox. The resuscitation of two servants asphyxiated by the fumes from a charcoal fire, the armless man who ate, drank, and played cards and dice with his feet, the girl of 15 who suddenly changed her sex—these are cases which might belong to any period of history. Most interesting of all, for the light which they throw on the character of their author, are Paré's accounts of his own illnesses and mishaps, including a compound fracture of the leg.

For clinicians searching for early records of conditions in which they are interested, this well-produced volume, with its clear lay-out, excellent index, and informative notes, should be a most useful guide.

F. N. L. POYNTER.

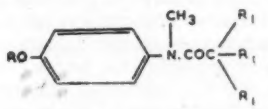
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

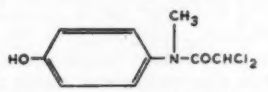
Diloxanide Furoate

"Furamide" (Boots).

Composition.—The manufacturers prepared a series of substituted acetanilides of the following type, where R is hydrogen or alkyl and R_1 is hydrogen or halogen:



These compounds were found to show considerable amoebicidal activity *in vitro* and some of them activity *in vivo* (in rats) against *Entamoeba histolytica*. One of the most actively amoebicidal was dichloracet-4-hydroxy-N-methylanilide (R.D. 3803), to which the name "entamide" was given:



Subsequently, for reasons mentioned below, modifications of diloxanide, such as the benzoate, the piperazine sulphate, and the furoate were prepared. On diloxanide furoate the name furamide was conferred; this compound is the subject of the present comment. It is put up in tablets each containing 0.5 g. of the drug.

Laboratory Testing.—Furamide is said to be many times more lethal *in vitro* to cultures of *Entamoeba histolytica* than was the parent substance or the other derivatives so far prepared from it. *In vivo*, in experimental animals treated orally, the furoate proved to be less toxic than the parent substance, itself of low toxicity; it was found to be absorbed from the gut to a lesser extent as estimated by blood-level determinations.

Therapy.—Several small groups of patients with intestinal amoebiasis, both symptomatic and asymptomatic, were initially treated with the parent substance, entamide. The cure rate among those with asymptomatic infections was reported to be good, but among those with symptomatic infections (amoebic dysentery) it was very unsatisfactory. For this reason modifications of the parent compound have been investigated.

Data are now coming to hand on similar clinical trials of furamide. These have been conducted not only in Great Britain but in widely separated parts of the African continent, in Asia, and in South America. Satisfactory response is reported in symptomatic intestinal amoebiasis (amoebic dysentery) after a five-day course of furamide. The dysentery ceased in the majority of these cases, and it appeared probable that parasitic cure also was obtained in many of them. Asymptomatic intestinal infections apparently are usually eradicated by a course of this drug. Commendable features of its use have been ease of administration and absence of toxic side-effects. It is the prominence of the latter which detracts so much from the value of emetine-bismuth-iodide (E.B.I.), which is still regarded by most British workers as much the most effective orally administered amoebicide yet available. E.B.I. in fact is an extremely efficient drug for the eradication of intestinal amoebiasis, and it provides a standard of comparison for all new drugs advocated for this purpose.

Published records of the results of treatment of various forms of amoebiasis with furamide are still scanty, but they are at least encouraging. Unfortunately they are seriously deficient in some respects, not least in the lack of proper information on the prolonged, frequent, and regular examination of stools by skilled persons which are so essential for a proper assessment of the curative (sterilizing) value of any amoebicide. Medical literature abounds with a succession of new drugs, each one claiming to offer a final answer to the therapy of amoebiasis. Before adding further to this list it would be wise to accept new preparations, such as this, as being worthy of further investigation and therapeutic trial under properly controlled conditions, including careful observation after treatment. Such control is not easy under conditions in which patients commonly default or are liable to reinfection—two factors which will swing the assessment from one extreme to the other. These conditions inevitably obtain in tropical countries when the indigenous inhabitants are the subjects of study.

N.H.S. Basic Price.—100 tabs., 30s. 8d.

The greatly increasing success of modern methods of treatment in preventing disabling chronic mental illness and furthering the rehabilitation and discharge of the long-stay patient is resulting in a decline in the total number of mentally ill patients in hospital at any one time, notes the *Annual Report of the Board of Control for 1959*. The total number of patients was 136,176 at the end of 1959, a reduction of 5,452 during the year. On December 31 last year there were 100,575 patients under care under the provisions of the *Lunacy and Mental Treatments Acts, 1890–1930*, as well as 34,506 under treatment in designated accommodation on an informal basis outside the provisions of those Acts. In addition there were 210 Broadmoor patients in mental hospitals and 885 in Broadmoor institutions. There were 95,350 admissions to designated mental hospitals in 1959, compared with 91,558 in 1958 and 55,856 in 1950. Admissions to all institutions and to private single care numbered 98,243 in 1959, an increase of 2,275 over the previous year. The first Commencement Order made under the Mental Health Act came into operation on October 6, 1959, and repealed those provisions of the Lunacy Act, 1890, which prohibited the admission of persons of unsound mind to designated psychiatric establishments on an informal basis outside the provisions of that Act. "This was an important development and it is satisfactory to record," states the report, "that during the short part of the year for which the Commencement Order was effective, 16,724 patients were received for treatment on an informal basis. This represents 17% of the total of all direct admissions to care during the year. In addition a further 69,854 were admitted as voluntary patients during the year; thus in 88% of all the direct admissions for treatment during 1959 compulsory powers were not used. There is every hope that this encouraging and long-established trend will continue." (H.M.S.O., 9d. net.)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

New Drugs for Respiratory Insufficiency

SIR,—Your annotation on new drugs in the treatment of respiratory insufficiency (December 31, 1960, p. 1943) gives a very fair introduction to dichlorphenamide and THAM (trihydroxymethylaminomethane), but I think that potential users of these drugs should be more strongly warned about some of the possible snags. In the case of dichlorphenamide, there are three points I would like to make. Firstly, it should be cautiously administered to patients with severe acidaemia due to respiratory failure because, whatever it does to the pCO_2, it is very likely to make the acidaemia worse. This risk will be less serious in patients whose respiratory acidosis is fairly fully compensated (i.e., the blood *p*H is not far below normal). Secondly, it is an oversimplification to say that this drug lowers the pCO_2. It may lower the pCO_2 measured in blood removed from the body, but the pCO_2 in the tissue cells is very likely to be greater during dichlorphenamide administration. Thirdly, the inhibition of carbonic anhydrase may cause the pCO_2 of blood removed from the body to be lower than it is in the body, because the time elapsing between sampling and analysis allows hydration of CO_2 to continue, thus lowering the pCO_2.[1] Rebreathing methods of estimating pCO_2 may therefore be preferable to arterial-blood measurements because they obviate this difficulty.

With regard to THAM, the risk of severe anoxia in patients with respiratory failure who are given this drug must be emphasized. If, in a patient with a low alveolar ventilation, CO_2 excretion through the lungs is reduced as a result of the administration of THAM, there may then be a maintenance of alveolar ventilation and therefore a reduction in pCO_2 and an increase in PO_2, or a maintenance of pCO_2 with a reduction in alveolar ventilation, and therefore a reduction in pO_2. It is not yet known which of these effects will be the more common, but, if the second one occurs to any extent, then patients receiving this drug who are already in respiratory failure and who are not receiving oxygen-enriched air will be exposed to very severe anoxia.

I apologize for making these points without supporting data, but the preliminary reports have already established that these drugs have such profound effects, indicating that they must be used with the greatest care. Until more is known, patients who receive them should preferably have their blood gases and *p*H carefully followed. Enthusiasm for the treatment of CO_2-retention must not be allowed to obscure the fact that the treatment of anoxia is usually a much more important problem in patients with respiratory failure. This remark is not, of course, meant to suggest that either of the two conditions should be neglected.—I am, etc.,

The Middlesex Hospital, London W.1. E. J. MORAN CAMPBELL.

REFERENCE

[1] Cain, S. M., and Otis, A. B., *J. appl. Physiol.*, 1960, **15**, 390.

Falling Asleep at the Wheel

SIR,—Everyone agrees that the number of road accidents is staggering, and that in spite of all deterrent publicity and legislation the number of killed and injured continues to rise. For a variety of reasons it is difficult to explain and reconstruct the course of events which precede serious collisions. Alcohol is rightly held to be responsible for many accidents, but I believe that the alleged "slowing down of reactions" is much overestimated as a cause of accidents.

Having myself driven for 30 years, seen a good many accidents, and thought about the physiological mechanics prior to the impact, I have come to the conclusion that falling asleep at the wheel must be by far the biggest cause of serious motor accidents. In very many cases nothing else could adequately explain the condition of and the situation at the impact; an accident in which a mother and two children were recently killed on the A4 road must, I believe, belong to the same group. I do not wish to exonerate drinking before driving—quite the contrary; I think severe legislation against this misuse is fully justified. I believe, however, that the mechanism leading to accidents after alcohol consists in its inducing sleep, particularly under the conditions of warmth and insufficient ventilation which prevail during winter nights when the car is driven with the heating switched on and the windows more or less closed. Every experienced driver knows the danger of falling asleep, and most of us have had the frightening experience of escaping an accident in the last fraction of a second when we have woken up "in the nick of time" after a second of unconsciousness.

The problem of falling asleep at the wheel is frequently discussed among drivers, and I have often been asked what remedies I could suggest to avoid it. Amongst the suggestions which I have heard about were: removal of shoes and driving in bare feet; rubbing in solid eau de Cologne over forehead and cheeks; smoking; "benzedrine" (amphetamine sulphate) tablets, etc. Driving without shoes is possibly the best of the suggested remedies. The only safe method of prevention, however, is to give strict instructions to drivers to stop the car in a safe place at the first sign of sleepiness and to try and find sleep. In the young, such sleep may last a considerable time; in middle-aged people sleep of a very few minutes is refreshing and completely dispels the feeling and the danger of impending sleep.

The purpose of this letter, Sir, is to suggest that sleep is the most frequent cause of grave motor accidents, although for various reasons people who were involved in such accidents may not care to admit this, may not even be aware of it themselves, or may no longer be able to say anything. In the present campaign for reduction of motor accidents the danger of sleep as a causative factor is badly neglected. The possibility of falling asleep at the wheel and meticulous prevention of this contingency deserve much more attention than they have hitherto received; all suggestions against it should be discussed, and reliable preventive methods recommended to the public.—I am, etc.,

St. James' Hospital, Balham, London S.W.12. A. B. ALEXANDER.

Epidural Anaesthesia and Bed Rest in Sciatica

SIR,—We read with interest the article by Dr. E. N. Coomes (January 7, p. 20) comparing a series of cases of sciatica treated by epidural injection with a similar series treated by bed rest. The most disturbing thing was to see how slowly the cases in the bed-rest group recovered, the mean time being four and a half weeks. This is contrary to our experience. We find that in those patients treated by us on bed rest at Sefton General Hospital, Liverpool, the pain had usually gone com-

pletely by the end of the first week, although it was usual to continue the bed rest for an arbitrary period of two weeks. Indeed, we find that those patients still complaining of pain at two weeks, or whose pain recurred on getting up at the end of this time, were usually those whose annulus fibrosus had actually ruptured or become irreparably stretched and who subsequently required operative treatment.

The discrepancy between our results of bed rest and those reported in the article would appear to lie in what is meant by the term "bed rest." Our patients were admitted to hospital, put in bed on fracture boards, and, in order to secure the most effective rest to the lumbo-sacral region, light-weight traction was applied to the legs. The patients referred to in the article were treated either in hospital without traction or at home, where, in the absence of full nursing care, bed rest can only be partial.

Epidural injection, with the volume of fluid used for the treatment of sciatica, is in our limited experience a painful procedure and cannot be considered to be entirely without risk; furthermore, it is illogical to believe that it can cure those cases of sciatica due to rupture of the annulus fibrosus. We feel very strongly, therefore, that bed rest with traction is the conservative treatment of choice in cases of sciatica due to prolapsed intervertebral disk, and that, where this fails to achieve cure within a reasonable time, then the disk should be removed at operation.—We are, etc.,

F. C. DWYER.
Liverpool. F. HOWARD BEDDOW.

Influenza During Pregnancy

SIR,—Your annotation on influenza in pregnancy (January 14, p. 114) will perhaps remind those of your readers who are interested enough that two years ago the *B.M.J.* (March 22, 1958, p. 695) advised parents who had had an anencephalic child to restrict conception to the winter months. It is fairly certain that the vast majority of those unfortunate parents to whom this somewhat austere advice was offered never even knew it existed, and, if they did, what were they to do in the spring, the summer, and the autumn?

In 1959 your columns provided much interesting reading on the advisability of therapeutic abortion in early pregnancy complicated by rubella, and Dr. Julia Bell[1] set about a distinguished London practitioner with all the statistics she could muster, and they were obviously formidable. Subsequently in your correspondence columns she was given some very rough handling by individuals whose motives were not always actuated by an intense interest in Dr. Abercrombie's unfortunate patient or of her potentially deformed child. In retrospect, I think Dr. Abercrombie will readily concede that the case of the lady mentioned in the fifth James Mackenzie lecture[2] was perhaps mismanaged, and to some extent Dr. Bell's criticisms were justified. On the other hand, some of her "suggestions for the G.P." were given so authoritatively as to resemble an Act of Parliament or an Army order.

Last year matters took a more sober turn, and Professor Jeffcoate's account[3] of the present position as regards the indications for therapeutic abortion, presented with a clarity of expression to which those of us who know him well have long been accustomed, drew little comment in your columns, and on the particular aspect of whether therapeutic abortion should be induced in every case when a woman acquires rubella during the first three months of pregnancy his remarks, though made admittedly from the standpoint of a clinician, were eminently sound, humane, and practical. Dr. Bell would have done better to remember that, though the statisticians may shuffle unfortunate patients and their unborn children like cards, they often fail to deal us a playable hand.

Also a year ago Dr. M. J. Pleydell[4] published an epidemiological study of anencephaly from the county of Northamptonshire. From the examination of some 60,000 live births he extracted 85 anencephalics, rather less than my own series of 92,000 live births with 260 anencephalics.[5] He made some very dogmatic statements on the influence of environmental factors in the incidence of anencephaly, which, by comparison, left my own simple conclusion, "Anencephaly appears to have a very constant incidence, which seems to be unaffected by locality, parity, and maternal age. The absence of positive differences shows that at the moment, and so far as present knowledge goes, no environmental factor can be held responsible for its incidence, and, this being so, the question of whether anencephaly is due to hereditary or genetic factors alone is still *sub judice*," very far behind.

This year your annotation is helpful and statesmanlike, in that it takes the matter soberly just about as far as present knowledge still permits us. Wise individual assessment by the usual practitioner in association with a sound and resolute obstetrician, upon whose judgment by long experience he knows he can rely, will surely see most women thus stricken through what must inevitably be a most harrowing experience.—I am, etc.,

Liverpool, 1. H. VINCENT CORBETT.

REFERENCES

1. Bell, Julia, *Brit. med. J.*, 1959, **1**, 686.
2. Ibid., 1958, **2**, 1349.
3. Jeffcoate, T. N. A., ibid., 1960, **1**, 581.
4. Pleydell, M. J., ibid., 1960, **1**, 309.
5. Corbett, H. V., *J. Obstet. Gynaec. Brit. Emp.*, 1953, **60**, 907

Fibrinogen Estimation

SIR,—May I commend Dr. Roy M. Calman and Mr. P. G. Cole's article (December 31, p. 1933)? They rightly stress the importance of serial estimations of blood fibrinogen in haemorrhage associated with childbirth. As a pathologist I feel that the rough and ready bedside test—whether 1 ml. of patient's blood clots within 10 minutes in a test tube—is unsatisfactory and may be misleading. Blood clots in a test tube when the fibrinogen is 100 mg. per 100 ml., and a gelatinous clot forms in 10 minutes even when the fibrinogen is 60 mg. per 100 ml.[1] Whenever there is time, a blood-fibrinogen estimation should be done at the first sign of haemorrhage and repeated at hourly intervals if the bleeding continues. The first finding may be 400 mg. of fibrinogen per 100 ml., the next 300 mg., and the next 200 mg. If the clinical condition warrants it, it may be wise to give intravenous fibrinogen rather than wait till the blood fails to clot. To withhold fibrinogen in these circumstances may be a terrible and tragic mistake.

In the article it is stated that fibrinogen "should not be administered unless really required." May I question this? It is surely far better to give fibrinogen rather than to withhold it if there is the slightest danger of death from haemorrhage. The danger of giving fibrinogen—assuming the danger of air embolism due to frothing is guarded against—is less than that of blood. There is no danger of blood incompatibility, no danger of potassium or citrate poisoning, and no danger of overloading the heart. The only dangers are the remote risk of homologous serum jaundice and infection. It

has been said that fibrinogen should only be used when absolutely necessary because it is in short supply. However, quadruple-strength dried plasma (not serum) can be used and contains about 4 g. of fibrinogen. Dried plasma is not in short supply.

We all prefer techniques to which we are accustomed. May I suggest that Stirland's heat turbidimetric method[2] is simple, quick, and easy.—I am, etc.,

Pathology Department,
Worthing Hospital, Sussex. R. AIDIN.

REFERENCES

[1] FitzGerald, T. B., and Jackson, S. H., *Lancet*, 1956, **1**, 412.
[2] Stirland, R. M., ibid., 1956, **1**, 672.

Clinic Doctors

SIR,—Being a "clinic doctor" within a year of retirement and having brought up four children, the eldest of whom is a nurse, and another a doctor, I am rarely disturbed by the disparaging remarks of members of the profession regarding those of us who devote our lives to a cause which we consider worth while, and in commenting on the letter by Drs. N. R. Garden, Bridget K. Attlee, and Rosemary M. W. Ince (January 14, p. 132), if I may be briefly personal, I cannot believe that the small offering I have made to medicine in bringing the experience of motherhood backed by a medical training has in any way been harmful or redundant.

It is the gross pomposity and complete lack of appreciation of work really done in the field of preventive medicine which this letter reveals that prompts me to answer in no uncertain terms. There are many ways of serving humanity, some more spectacular than others, but the signatories of the letter referred to above would do well not only to cultivate a spirit of humility which would enable them to recognize value in fields other than their own, but before going into print to take the trouble to get their facts correct. A wise and experienced "clinic doctor" spends much of her time doing child-guidance work. It is not necessary for every enuretic, temper tantrum, head-banging child to be referred to a psychiatrist, nor is it the practice to inundate the overworked general practitioner with behaviour and feeding problems which one hopes are solved or helped at the clinic.

It is of some interest to note that Drs. Garden, Attlee, and Ince cannot see the justification for the existence of the "clinic doctor"; it is to be hoped that they can justify their own.—I am, etc.,

Basingstoke, Hants. HILDA M. PRICE HUNT.

SIR,—Drs. N. R. Garden, Bridget K. Attlee, and Rosemary M. W. Ince (January 14, p. 132) are to be congratulated on their outspoken and succinct commentary on the public health contribution to infant welfare and child health. This is a field surely richly rewarding and wholly satisfying to the genuine family practitioner who wishes to be completely responsible for his patients in a sphere where so much can be achieved in initiating and preserving a harmonious patient–doctor relationship.

I speak with both feeling and experience on this matter, having been concurrently general practitioner and part-time school medical officer cum child welfare clinic doctor. In the latter two capacities I saw conditions which were eminently family practitioner work and I took great pleasure in passing back to my colleagues in general practice all cases requiring any kind of treatment other than reassurance, together with a personal communication. From discussions with regular full-time school medical officers and child welfare clinic doctors I have formed the opinion that their work can be done much more efficiently by practising family doctors and at much less cost to the country.—I am, etc.,

Ipswich, Suffolk. C. F. R. MALLETT.

SIR,—With regard to the letter headed "Clinic Doctors" (January 14, p. 132) it would be unfruitful to try to answer all the curious charges which Drs. N. R. Garden, Bridget K. Attlee, and Rosemary M. W. Ince bring against their medical colleagues who staff local authority clinics—as, for instance, the villainy of encouraging mothers to bring babies to clinics by "the presence there of a doctor . . . cheap milk, 'marmite,' 'bemax,' orange juice, and vitamins."

The major misconception appears to be a complete misunderstanding of the functions of public health officers. Such doctors (from the M.O.H. downwards) are occupied in trying to prevent disease and illness, not in curing it after it has occurred. This is the presumed function of the hospitals and general practitioners. The doctor at a baby clinic is primarily occupied in seeing healthy children, and is on the look-out for defects which, because the child is not ill, may never be noticed by the family doctor until the child happens to be taken to see him for something or other—defects which needed treatment at the earliest moment. In this connexion I need only refer your correspondents to one of the leaders in your same issue on the importance of recognizing early squint in young infants (p. 112), the tendency some mothers have to think it will get better spontaneously, and the regrettable consequences of this. Such a child—a healthy child—will be more likely to be noticed by the clinic doctor on routine examination than by its own doctor, simply because it does not occur to the mother to visit him. Indeed, the condition has to be pointed out to her, at the routine examination, before she realizes anything is wrong. The same holds good of routine examination in young infants for congenital dislocation of the hip, a condition which is not self-evident before the child walks, does not make it ill, and so passes unnoticed until cure is made much more difficult. One could multiply instances, but these two should suffice.

As to saying that "the clinic doctor is well advised not to give any advice on his findings," one wonders whether your correspondents realize that "clinic doctors" have also qualified in medicine, are on the *Medical Register*, and have, one would suppose, as much right to give advice if asked for it as has anyone else. Furthermore, it is roughly true that the public knows what is good for it; if it attends clinics and asks for advice, the presumption should be, one would think, that it finds the advice it gets from that source helpful and useful. Finally, the extraordinarily ill-natured crack about clinic doctors being "well paid" comes badly from doctors who have just accepted a £500-a-year rise in their own salaries whilst passively agreeing that the Royal Commission which awarded it to them should not even begin to consider the claims of their public health colleagues.—I am, etc.,

Aspley, Nottinghamshire. ALISON M. HAMILTON.

Fainting and Dental Anaesthesia

SIR,—The main danger with nitrous oxide in dentistry is fainting,[1 2] and many cases of severe cerebral anoxia might be prevented if dentists and dental anaesthetists were warned of this danger, so that they could get the patient down flat at the very first sign of trouble and not waste time giving oxygen until this had been done.

It may now be asked, Will the same danger arise with cyclopropane? This question is important because simple apparatus for the widespread trial of cyclopropane in dentistry will soon be available. I concluded[2] that the dental anaesthetist should be constantly on the watch for fainting, and no less so with cyclopropane than with nitrous oxide. The nigger in the woodpile is the upright position of the patient, and I believe that fainting will be a danger in dental practice with any anaesthetic so long as we continue to give the anaesthetic with the patient sitting up.—I am, etc.,

St. Thomas's Hospital, London S.E.1. J. G. BOURNE.

REFERENCES

1 Bourne, J. G., *Lancet*, 1957, **2**, 499.
2 —— *Nitrous Oxide in Dentistry: Its Danger and Alternatives*. 1960. Lloyd-Luke, London.

Infectious Mononucleosis

SIR,—You state in your leading article (January 14, p. 111) on infectious mononucleosis that "patients may present with mild fever, slightly enlarged posterior cervical or other glands, and perhaps slight sore throat, but can hardly be diagnosed without a white blood count . . ." However, I feel it is also important to stress that the early appearance of palatal petechiae is pathognomonic. In fact I have seen these petechiae as the only evidence of "glandular fever," and where later blood examination was confirmatory.

I also note that many medical textbooks fail to mention this important physical sign.—I am, etc.,

The Middlesex Hospital, London W.1. D. P. MULLAN.

SIR,—Having been interested in glandular fever for many years, I was naturally attracted to your leading article (January 14, p. 111). The suggestion[1] that the disease has three phases, each associated with a progressively rising Paul–Bunnell titre, cannot go unchallenged. I am surely not alone in my experience when I say that the titre of the Paul–Bunnell test bears no relationship to the stage or severity of the disease. May I quote a few personal cases?

B.J., female, 17 years. Ill for two weeks. T. 103° F. (39.4° C.). Large membrane-covered tonsils. Submandibular swelling. Large spleen. White cells 9,000. Mononuclears 88%. Paul–Bunnell test 1 in 64.

D.N., male, 16 years. Sore throat one week. T. 99.8° F. (37.7° C.). Large red tonsils—no membrane. Palpable spleen and axillary glands. White cells 18,000. Mononuclears 74%. Paul–Bunnell test 1 in 512.

G.A., male, 10 years. Abdominal pain sudden in onset and mimicking acute appendicitis. T. 101° F. (38.3° C.). Not ill. Only one cervical gland palpable. No signs elsewhere. White cells 7,700. Mononuclears 40%. Paul–Bunnell test 1 in 1,024.

J.G., female, 19 years. Sore throat for two weeks. T. 99° F. (37.2° C.). Large tonsils covered with yellow membrane. Generalized lymph-gland enlargement. White cells 7,900. Mononuclears 70%. Paul–Bunnell test 1 in 160.

V.v.S., female, 17½ years. Sore throat for three weeks. T. 98° F. (36.7° C.). No gross physical signs in any system. White cells 7,100. Lymphocytes 37%. Paul–Bunnell test (absorbed) 1 in 320.

In common with others, I have examined the serum electrophoretic patterns of these and other patients, hoping that not only would I find a constant abnormality but that this would be related to the Paul–Bunnell titre. I have been disappointed. All four fractions (α_1, α_2, β, γ) rise and fall indiscriminately and bear no relationship to the Paul–Bunnell test except that serum changes occur in all positive cases, and that they remain for periods of one year or so, long after the test has reverted to negative. Both the mechanism and the positive relationship of the Paul–Bunnell test remain as yet unexplained. Much more work remains to be done before a hypothesis of phases can be accepted.—I am, etc.,

Chadwell Heath Hospital, Romford, Essex. I. M. LIBRACH.

REFERENCE

1 Evans, A. S., *Amer. J. Hyg.*, 1960, **71**, 342.

ABO Groups and Peptic Ulcer

SIR,—I was very interested to read Mr. Ernest W. Grahame's paper on this subject (January 14, p. 95). He may have missed my own paper of 1957[1] recording somewhat similar findings. I showed then that an analysis of 523 cases of gastric ulcer suggested that prepyloric ulcers, and gastric ulcers which had developed upon a basis of old duodenal ulceration, had a preponderance of group O similar to that reported for duodenal ulcer. I suggested that this fact might, indeed, be sufficient to explain the whole of the relatively smaller preponderance of group O among gastric ulcers of all types together (as against duodenal ulcers). I also emphasized that the results of analysis of such small groups could only be "pointers," indicating the desirability of further collection of material. It is particularly interesting that this second similar analysis has pointed in the same direction.—I am, etc.,

London W.1. H. DAINTREE JOHNSON.

REFERENCE

1 Johnson, H. D., *Lancet*, 1957, **2**, 518.

Radiological Hazards to Patients

SIR,—Under this rather inappropriate title "Anonymous" (December 24, p. 1881) has stirred up a hornets' nest and a correspondence of importance.

First let me say that I am in favour of ancillary methods of investigation being made accessible to general practitioners, as they are in this area, and the practice will inevitably become general. But it would surely be wiser before these costly, and often misleading aids to diagnosis are made freely available that there should be more grounds for believing that the practitioners employing them know how to evaluate the results and assess the limitations of the techniques employed. This knowledge is not to be obtained at present as a student, or even after three or four resident posts, nor can the average general practitioner gain enough experience by learning from his errors except over many years. Something more should be done to instil this knowledge at student and resident level for

the future, and by gentle persuasion at postgraduate courses and local meetings for those already qualified.

Too often at present a minority of doctors—but a substantial one—arrange a chest film, or blood count, for a patient complaining of fatigue, without doing the most essential investigation of all, a full history and complete physical examination. The patient feels happy, science has been applied; the doctor presumably feels happy until, three months later, with now obvious weight loss, the patient arrives too late at an out-patient clinic with advanced disease. How dangerous negative reports can be, and none more so than the normal barium meal in the middle-aged with a short dyspeptic history, a finding which should evoke intensive investigation rather than relief and inactivity.

What follows does not imply disrespect for radiologists, to whose reports we attach great weight, but I know that all too few practitioners examine the films of patients they refer to *x*-ray departments. It is, of course, essential that the clinician should see his patient's films. There are several reasons for this, the clinician knows what he's looking for, and even with that rarity, a full summary, he may have failed to transmit this point adequately to the radiologist. The radiologist will be expert in most fields of radiology but not usually in all, and here the clinician may be able to fill in the gap. Radiologists are human, too, and not rarely miss things that a second pair of eyes will detect. Finally, to state the obvious, pressure of work and the quality, and above all the quantity, of staffing in peripheral ancillary departments will vary and so produce results of varying reliability, something that the doctor fresh from more fortunately appointed teaching hospitals and with an overdeveloped belief in the infallibility of "scientific medicine" may take time to get used to.—I am, etc.,

Ipswich, Suffolk. J. W. PAULLEY.

Prolonged Survival with Pulmonary Metastases

SIR,—Extensive pulmonary metastases usually imply a rapid downhill course. That this is not always so is illustrated by the case described below. The patient has had multiple metastatic deposits in the lungs, from a carcinoma of the body of the uterus, for four years and has remained almost free of pulmonary symptoms.

In February, 1955, at the age of 54, she attended Hammersmith Hospital with a history of post-menopausal vaginal bleeding for one year. Examination revealed a large bulky uterus and a 2-cm. nodule in the vaginal wall near the introitus. Curettings of the uterus and biopsy of the nodule both showed well-differentiated adenocarcinoma with few mitoses. *X*-ray of the chest at this time showed no abnormality. Treatment by intracavitary radium and radium needle insertion was given. In October, 1956, there was local recurrence in the vagina, and this was treated by a further radium needle insertion. A routine chest *x*-ray at this time (Fig. 1) showed a small round opacity in the fourth right space anteriorly and another one near the right costophrenic angle suggestive of metastases. There were no chest symptoms. In September, 1958, she developed pain in the right lower ribs and a chest *x*-ray (Fig. 2) showed extensive bilateral secondary deposits in the lung fields. The chest pain cleared up spontaneously. In July, 1960, she again developed intermittent pain in the chest. This was very slight and there were no other pulmonary symptoms. A chest *x*-ray (Fig. 3) revealed that the metastatic deposits had enlarged and become cavitated in the right lower zone. There were also bony deposits in the pelvis and both femora and there was recurrence in the labia majora. At no time had she any radiotherapy to the lung fields, or any chemotherapy.

It is important in assessing the results of therapy in advanced malignant disease to remember the wide variation in the natural history of the condition. Prolonged survival of patients suffering from untreated extensive disseminated cancer has been reported in a number of cases. For example, Cameron[1] described a woman of 40 with carcinoma of the breast who had "recurrent nodules on the chest wall, hard cancerous glands in the supraclavicular fossae, and unmistakable signs of disease in the dorsal vertebrae" and who lived six years without treatment and died from an accident. Boyd[2] believes that a partial immunity against malignant disease may exist in some patients. This hypothesis may well explain the exceptional behaviour of malignant tumours that one occasionally sees in radiotherapeutic practice.

I would like to thank Dr. L. H. Walter for permission to publish details of this case.

—I am, etc.,

Radiotherapy Department, Hammersmith Hospital and Postgraduate Medical School, London W.12. MAURICE SUTTON.

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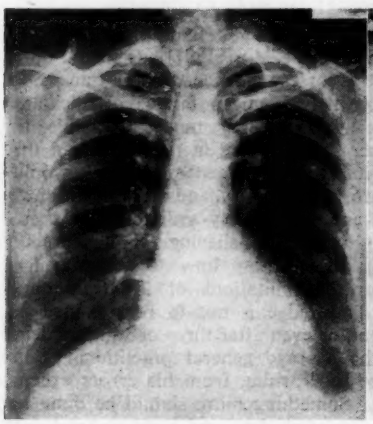

FIG. 1

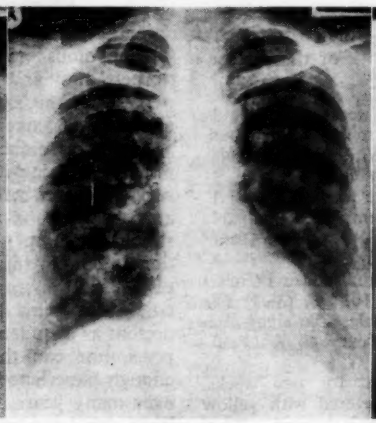

FIG. 2

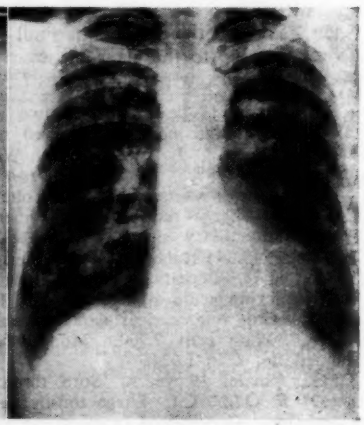

FIG. 3

Is Thalidomide to Blame?

SIR,—We are interested to read the letter by Dr. A. L. Florence (December 31, p. 1954) concerning neurological symptoms in patients receiving thalidomide ("distaval"), since we have five similar cases under investigation. We have provisionally attributed the symptoms to peripheral sensory neuropathy, but our studies are not yet complete. Now that attention has been drawn to these cases we hope to obtain more for detailed study.—We are, etc.,

E. V. KUENSSBERG.
J. A. SIMPSON.
J. B. STANTON.

Neurological Unit,
Northern General Hospital,
Edinburgh 5.

Nurses (Amendment) Bill

SIR,—I am surprised that the Nurses (Amendment) Bill published in December has not been the subject of comment in either the editorial or correspondence columns. This Bill reflects the thoughts of the General Nursing Council and has the support of members on both sides of the House. Its main purpose is to drop the word "Assistant" from the term "State Enrolled Assistant Nurse." This is excellent as far as it goes, but unfortunately it does not go far enough. The enrolled nurse, irrespective of her intelligence and ability, will not be eligible for promotion. Hers will still be a dead-end job.

In the not too distant future the enrolled nurse is to be the practical bedside nurse on whom our hospitals will have to rely for the majority of their nursing staff. The registered nurse is to be the leader, the responsible nurse, ward sister, etc. The army of hospital nurses is to be composed of privates and officers, and there will not even be the equivalent of non-commissioned officers.

One grade, the private, is to be trained in practical nursing; the other, the officer, recruited from different schools but not necessarily of higher intelligence, is to be trained in both theory and practice. Why shouldn't both grades do the same practical training? State Enrolment would then be the first step towards registration. This simple procedure would overcome many of the objections which have been made to the proposals of various committees advising on the future of nursing. Small nurse-training schools, at present threatened with closure, would continue more or less in their present form but training only to State Enrolment standard. This would not diminish the number of potential recruits for registration, there would be no danger of a caste system developing, and it would unify the profession, whereas the present proposals of having two distinct types of nurse will split the profession completely.—I am, etc.,

Banbridge. H. W. GALLAGHER.

Epidemic Bronchiolitis

SIR,—In your leading article on epidemic bronchiolitis (December 24, p. 1863) you suggest that the term "epidemic bronchiolitis" would seem to be the most satisfactory from both a pathological and clinical point of view. A similar emergence of a well-defined entity bronchiolitis from a terminological hotch-potch is noted independently in a recent annotation in the *Lancet*.[1] Heycock and Noble,[2] whom you quote, "advance a tentative theory that acute bronchiolitis is not distinguishable from bronchopneumonia." All this seems to imply that this entity has only recently become clarified. Such an implication, however, is without foundation.

Anyone who cares to read the exhaustive clinical and pathological studies on pneumonia in childhood from Edinburgh by McNeil, MacGregor, and Alexander[3] carried out over 30 years ago, and published in one of your own specialist journals, would learn that such an entity was clearly recognized clinically and pathologically about 1850 by Barthez and Rilliet. They used the term bronchopneumonia and considered that capillary bronchitis and bronchopneumonia were indistinguishable. The Edinburgh group quoted above did not find any difficulty, either clinically or pathologically, in recognizing such an entity. They described 140 cases under such a term.

The persistence of terminological hotch-potch is only helped by lack of proper perspective, even in such widely acclaimed journals as yours and the *Lancet*. It is bad enough when American writers tend to ignore British works, but neglect of our own work by our own reviewers is indefensible. It appears that the only "advance" made in our knowledge is that what was bronchopneumonia in 1850 is now bronchiolitis in 1960.—I am, etc.,

Taylor Research Laboratory,
Children's Hospital,
Sheffield. AVINASH MITHAL.

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"Virugon" in Respiratory Diseases

SIR,—The General Practitioner Research Group[1] in their first report on general-practitioner clinical trials present the drug known in Sweden as "flumidin" and in England as "virugon"[2] as being of potential interest as an anti-viral agent. In contrast to the positive findings reported by several investigators are the results by Dr. G. I. Watson (December 17, p. 1785) of the failure of virugon to benefit the course of non-bacterial infections of probable viral origin. According to information presented in the literature and recently at the Conference held in Stockholm on ABOB and flumidin, the overwhelming amount of experimental and clinical evidence shows ABOB (N^1,N^1anhydrobis (β-hydroxyethyl) biguanide hydrochloride) to possess anti-viral effect directed especially against influenza of various types. Since this is a new field for chemotherapy, it is essential to find the limitations of the new drug. This requires carefully conducted studies with appropriate controls, not only of the disease as such but also of strictly comparative control cases, for the evaluation of the drug's effect. Unfortunately Dr. Watson's very few cases seem to add nothing to our knowledge of the new drug, and to a health officer within a large industry Dr. Watson's way of selecting the material seems to throw doubt on the reliability of his conclusions.

As Dr. Watson points out, it is difficult to diagnose virus diseases outside epidemics. We have therefore concentrated on epidemic influenza as occurred in Sweden last winter. My group undertook to carry out a blind study with three different types of coded tablets, one a placebo, the second ABOB, and the third one the combination of flumidin (virugon). The study was started when influenza was already spreading in the factory and was carried out parallel to a vaccination study. Because of the swift outbreak of influenza the

vaccination did not give any protection at all. The two coded preparations containing the active drug both produced a significant protection against influenza as well as against the upper respiratory viral infection which appeared simultaneously but without all the typical influenza symptoms. This material, which I recently presented,[3] comprised 1,534 cases. According to my experiences no certain conclusions can be drawn from small exploratory studies like those presented by Dr. Watson.—I am, etc.,

JOHN HAGLIND,
Industry physician,
Volvo Köpingverken.
Köping, Sweden

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Placebos

SIR,—I was interested to read your annotation (January 7, p. 43). It is to be doubted, however, whether it is the wise physician who treats "as many patients as possible with the new drugs while they still have the power to heal." In many cases to-day it is to be hoped that the wise physician waits to see the results of treatment on patients not his own. These human guinea-pigs may reveal unpleasant side-effects and serious complications of the drug not previously suspected. In any case, I believe it is correct to say the advice was not given seriously but as an expression of contempt.

In the penultimate paragraph it is said that the placebo effect is not confined to medicine but that "treatment by the methods of physical medicine is found sometimes to be in this category, while even the rationale of some surgical operations has likewise been called in question." This is indeed a masterly understatement.—I am, etc.,

M. E. M. HERFORD.
Farnham Royal, Bucks

Barrier Creams

SIR,—Dr. F. Ray Bettley states (November 19, p. 1467) that emulsifying and wetting agents may all, in appropriate circumstances, increase the percutaneous absorption of foreign compounds, but Dr. L. B. Bourne (October 1, p. 1014) suggests that there may be uncommon emulsifying agents less likely to do so. We would draw attention to the non-ionic macromolecular emulgents (e.g., methylcellulose) which are unlikely to affect keratin chemically (thus contrasting sharply with the anionics[1]), are neutral in reaction, and are unlikely to act as sensitizing agents or to appreciably penetrate the epidermis.

The reported increased absorption of foreign compounds may be due to the use of barrier creams forming occlusive films in oils, long-chain alcohols and acids, etc., which, by retarding the evaporation of water,[2] would increase the hydration of the outer stratum corneum.[3–5] This hydration of the main barrier to percutaneous absorption[6 7] leads to increased penetration, especially by compounds soluble in oil.[3] Surfactants which have been shown to increase the rate of transport of potentially irritant, allergenic, or toxic compounds would further increase the possibility of reactions.

Occasional unsatisfactory results with some silicone creams may be due to their containing surfactants which assist the transport of compounds across the outer keratin. Since many compounds are insoluble in silicone fluids, these latter, emulsified with methylcellulose, seem preferable to mineral and vegetable oils as barrier agents, and both have the further advantage that, since they permit the passage of water vapour, hydration of the stratum corneum is not appreciably increased. We therefore formulated the following barrier lotion (in which dimethicone is incorporated in methylcellulose solution by mechanical stirring and subsequent homogenization):

Dimethicone 20 B.P.C.	30%
Methylcellulose 20 B.P.C.	4%
Preservative	q.s.
Water	to 100%

A mixture of methyl hydroxybenzoate B.P.C., 0.12%, and propyl hydroxybenzoate B.P.C., 0.03%, is suitable as a preservative, and 2-phenyl ethanol, 0.5%, is also satisfactory. The lotion is cheap, pharmaceutically elegant, and contains only official B.P.C. constituents. Satisfactory preliminary clinical trials have shown the residual film to be non-slippery (of value to laboratory and similar workers), and transfer of silicone to handled material such as paper is minimal.—We are, etc.,

M. A. COOKE,
Medical Adviser,
Albright & Wilson (Mfg.) Ltd.
Oldbury, Worcs.

A. P. LAUNCHBURY,
Pharmacist,
The Skin Hospital, Birmingham
Birmingham 15.

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Service Overseas

SIR,—In the past year Lord Twining and many press articles have drawn attention to the continued need for British-trained, professionally qualified people to serve overseas. Mr. Julius Nyerere's recent speech in the Tanganyika Legislature was a further appeal to this end, and the Prime Minister and the Secretary of State for the Colonies, speaking at the diamond jubilee dinner of the Corona Club last June, mentioned improved conditions of service for members of the Overseas Civil Service, which I have since seen translated into effective action. There seems no reason, therefore, for any lack of support from the medical profession. Teachers are already setting up efficient and useful exchanges of personnel. Professor K. R. Hill's article (January 14, p. 117) is, however, the first constructive approach I have seen from within the profession, and, except on one or two points, I am in full agreement with his conclusion that a central medical council to deal with all overseas medical personnel is required. This body should be empowered to liaise with the overseas country to secure uniform conditions and codes of practice.

It seems to me that there is no lack of potential recruits, and a central organization to which those who have special aspirations, aptitude, or ability can apply and receive authoritative advice is essential. I find it disappointing, for example, to observe that the first four Nuffield travelling fellowships for general practitioners

should be to the much-visited U.S.A. and Canada. No doubt the adverse reports in the medical press about the irritations encountered during service abroad are a reason for avoiding the former colonies now emerging to self-government. These reports are, however, hardly ever refuted or discussed, and, while not disputing the integrity of such letters, it is only fair to point out that it is unlikely that anyone can expect to get more out of this type of service than they put into it.

In my opinion the permanent medical directorate of Professor Hill's proposed Commonwealth Medical Council should be a Government department staffed by experienced medical advisers from the Ministry of Health, the Colonial Office, the Commonwealth Relations Office, and the Foreign Office. The membership of the council itself might include all Government departments and organizations who send medical personnel overseas, such as H.M. Forces, the British Council, missionary societies, and industrial firms, etc. The B.M.A. might wish to be represented, but a semi-voluntary organization under the auspices of the B.M.A. in my view would not carry the central governmental authority and political awareness to make the work effective at home and abroad. If the plans are made and implemented within the framework of such a council, British doctors would have a tremendous opportunity to show their mettle and help to avoid the experiences which have dismayed us all in the Belgian Congo. The history of British medicine overseas is, to say the least of it, a fine one, and it would be a sad affair if the doctors of to-day, cosy in their successful N.H.S., were to allow foreign doctors and scientists to usurp their record in this particular field.

Personally neither I nor my family have the slightest regret for my tour of duty in the Colonial Service. We enjoyed it all and I gained considerable valuable experience. I did not find it difficult to re-enter the N.H.S., but must admit that I think I would have been more useful abroad with experience of the N.H.S. behind rather than in front of me. Given the proper organization and encouragement, the young doctors of to-day could be one of our most valuable exports, especially to Africa, if terms like good will, service, human relationships, help to the sick and needy, and the example of the British way of life are to mean anything at all in the vast reorganization that is happening now.

The best age for the doctor to do this service is when he and his family are fairly young. Children thrive in hot climates until they are 6, education is not a serious problem, and the wife gets plenty of willing help. At the end of one or two tours a decision has to be made whether to return home or stay, but appointment to a post at home need cause no anxiety if conscientious and efficient work has been done. The return to the young doctor in terms of experience, broadening of outlook, and self-confidence is far greater than anything which can be obtained in a comparable time in England to-day. —I am, etc.,

Syston, Leicester. J. A. WARD.

SIR,—In my letter in your issue of December 17 (p. 1801) I made a statement which was in error. The Nigerian Widows' and Orphans' Fund entitled pensions have not in fact been halved or reduced in any way for paid-up members. The information received by us was given in all good faith and was in fact checked by cable. I am very pleased to be able to say that this information was in fact false and regret any alarm which may have been caused by it.—I am, etc.,

Nairobi. P. E. C. MANSON-BAHR,
Chairman, Services Subcommittee of the B.M.A. Kenya Branch.

Splenic Rupture in Leukaemia

SIR,—We are interested in the description by Mr. M. J. Flood and Mr. R. A. Carpenter (January 7, p. 35) of a patient with acute myeloid leukaemia who had ruptured his spleen.

In July, 1959, we treated a man of 34 who had a spontaneous rupture of his spleen, and on further investigation was found to be suffering from chronic myeloid leukaemia. On direct questioning he denied any injury, but admitted to "a touch of malaria" in 1948 when in Malaya. On admission to the Mansfield Nursing Home he gave a history of recent tiredness and of 48 hours' abdominal pain which started in the left side of the abdomen and later became generalized. On examination, he looked ill and lay still. His temperature was 99.2° F. (37.3° C.), pulse 112, blood-pressure 140/80. His tongue was furred. The abdomen was slightly distended, with generalized release tenderness and rigidity of the left upper quadrant. The bowel sounds were diminished and there was rectal tenderness. His haemoglobin was 87% and there was slight anisocytosis and poikilocytosis seen on the film. Under a general anaesthesia given by Dr. A. G. Hegarty, the enlarged spleen could be felt. At laparotomy the spleen was found to be ruptured along its free edge and there was over one pint of blood free in the peritoneal cavity. Dr. A. B. Hill reported that the changes in the excised spleen and the liver biopsy were suggestive of granulocytic leukaemia. The total peripheral nucleated white-cell count was 300,000 per c.mm., of which about 14,000 were blast cells. This information was not available at the time of operation. The patient has remained well and has been on intermittent busulphan therapy since his splenectomy.

Two other uncommon modes of presentation of leukaemia have been seen by us. The first was an old lady who presented with an anal ulcer and was found to have an enlarged spleen and myeloid leukaemia. The second was an apparently healthy man of 36 who presented with painless haematuria and was found on examination to have petechiae on the right shoulder. Cysto-urethroscopy while bleeding showed a bloody efflux from both sides. He was found to have an acute leukaemia, blast cells forming 73% of the white-cell series in the sternal-marrow examination. He died one week later from a cerebral haemorrhage. Gastro-intestinal bleeding associated with leukaemia has occurred in 3 of our last 700 admissions for haematemesis and melaena.—We are, etc.,

J. C. PEASE.
J. N. WARD-MCQUAID.

Mansfield and District General Hospital, Notts.

SIR,—I was very interested to read the case of spontaneous rupture of the spleen in acute myeloid leukaemia described by Mr. M. J. Flood and Mr. R. A. Carpenter (January 7, p. 35), having encountered a similar case.

A 40-year-old man presented himself in the casualty department, complaining of abdominal pain. He collapsed while waiting and died almost immediately. On post-mortem examination, the only abnormal features were pallor of the body and a ruptured spleen, with a large amount of blood in the abdominal cavity. The spleen was enlarged about three-fingerbreadths below the costal margin. On histological examination, sections of spleen revealed a picture of acute myeloid leukaemia, which was also confirmed by peripheral blood and bone-marrow examination. So far as I could ascertain, there was no history of injury or trauma before his visit to the casualty depart-

ment, and his only complaints were some shortness of breath and feeling off-colour for a few weeks.

I have also been told of a similar case where only a post-mortem examination revealed the real cause of death. As neither case was published, I would infer that spontaneous rupture of the spleen in acute myeloid leukaemia occurs more commonly than suggested by the authors.—I am, etc.,

R.A.F. Hospital, Wroughton, Wilts. A. TALERMAN.

Phenylbutazone and Leukaemia

SIR,—We were interested to read the article by Dr. R. H. D. Bean, "Phenylbutazone and Leukaemia" (November 26, p. 1552), and also the letter by Dr. A. Lawrence on this subject (December 10, p. 1736). Although blood changes complicating phenylbutazone therapy are well recognized, there has been only one report of transient leucopenia complicating therapy with hydroxyphenylbutazone ("tanderil," G27.202).[1] This drug has previously been shown to have a similar anti-rheumatic and analgesic effect to phenylbutazone[2] but apparently less toxic side-effects.

We have recently seen a man aged 62 years who developed transient leucopenia and thrombocytopenia while on hydroxyphenylbutazone therapy. He was first seen in June, 1959, complaining of episodes of pain, swelling, and redness of both big toes, which settled spontaneously but were soon followed by an acute arthritis of the left knee, which was relieved within twelve hours of starting colchicine therapy. The serum uric acid level was 17 mg./100 ml., and a diagnosis of gout was made.

A routine blood-count showed: haemoglobin 19.3 g./100 ml. (132% Haldane), haematocrit 58%, with normal white cell and platelet counts. Polycythaemia was suspected and confirmed by the demonstration of an increased red-cell mass, using a ^{51}Cr technique. It was felt that the hyperuricaemia was attributable to the polycythaemia. The patient was venesected twice and received two one-month courses of busulphan between September and November, 1959, with temporary suppression of the white-cell count but no effect on the platelet count or haemoglobin level. Maintenance therapy with soluble aspirin relieved his joint pains but caused dyspepsia. In December treatment with phenylbutazone, 400 mg. daily, was commenced, but this also caused epigastric pain and diarrhoea. As a supply of hydroxyphenylbutazone was available and preliminary reports had suggested that it was efficacious in gout, this was substituted in a dose of 300 mg. daily, later reduced to 200 mg. because of further diarrhoea. As this produced satisfactory relief of his joint pains it was continued for six weeks until thrombocytopenia and leucopenia were noted (see Table). The drug was immediately stopped, and within two weeks the white-cell and platelet counts returned to normal. Repeated monthly counts since this episode have been normal. Subsequently long-term uricosuric therapy with probenecid was begun.

Date	Haemoglobin (%) Haldane)	W.B.C. (per c.mm.)	Platelets (per c.mm.)	Treatment
14/9/59	128	5,600	157,000	Calcium aspirin 3·9 g./day
12/10/59	121	2,700	142,000	Busulphan, 4 mg./day Calcium aspirin 3·9 g./day
17/11/59	121	4,900	121,000	" 3·9 " "
15/12/59	119	4,100	119,000	Busulphan 2 mg./day Phenylbutazone 400 mg./day
5/1/60	121	4,900	117 000	G27.202 300 mg./day
15/2/60	125	4,800	78,000	Nil
19/2/60	126	4,600	63,000	Tabs. paracetamol 4–8/day
23/2/60	121	2,800	98,000	" " "
26/2/60	120	4,000	90,000	" " "
1/3/60	121	5 300	106,000	" " "
7/3/60	121	5 000	149,000	" " "
4/7/60	120	4,800	137,000	" " "

We feel that the episode of leucopenia and thrombocytopenia observed was due to the hydroxyphenylbutazone therapy. Since the course of phenylbutazone was terminated six weeks, and the course of busulphan three months, before the episode, it is felt that neither drug can be held directly responsible. It is conceivable that either, or both, of these drugs could have produced a minor degree of sustained marrow suppression undetectable in the peripheral blood, and that the additional suppressant effect of hydroxyphenylbutazone unmasked this. It is most improbable that the thrombocytopenia and leucopenia were due to an aplastic phase of polycythaemia vera[3] because it was of such short duration, recovery being rapid and maintained for six months.

The authors wish to thank Dr. P. Bauwens, Dr. J. L. Pinniger, and Dr. G. Wetherley-Mein for permission to publish, and Dr. W. S. Stoddart, of Geigy Pharmaceuticals Limited, for supplies of hydroxyphenylbutazone.

—We are, etc.,

St. Thomas' Hospital, London S.E.1. D. A. H. YATES. R. W. PAYNE.

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Natural Gas

SIR,—Mr. James Lawrie in his letter (December 10, p. 1735) criticizing my own (November 26, p. 1597) on the dangers of "re-formed" natural gas containing carbon monoxide, stresses the interchangeability of methods of suicide, which I had myself admitted. My main concern was with the high and growing incidence of accidental deaths due to coal-gas, an incidence which would be perpetuated if the latter were replaced by re-formed natural gas.

The possibility of replacing coal-gas by natural gas which has not been re-formed, and the advantages of such a replacement, are demonstrated by Gonzales *et al.*[1] who write:

"In New York City in 1950 and 1952 respectively, throughout the Boroughs of Richmond and Brooklyn, natural gas was substituted for the old illuminating gas which was manufactured from coal and contained CO as its chief ingredient. Natural gas contains methane (CH_4), 94.1%; ethane (C_2H_6), 3.6%; propane (C_3H_8), 1.0%; higher paraffin hydrocarbons, 0.7%; and carbon dioxide (CO_2), 0.6%. There is no carbon monoxide in natural gas, so that if it is inhaled directly with plenty of oxygen, the victim is not seriously affected but only rendered uncomfortable. Of course if the gas were inhaled in a closed chamber without oxygen, it would cause death from asphyxia like carbon dioxide. As it is rich in hydrocarbons containing much carbon, natural gas on combustion might form considerable carbon monoxide and be a source of poisoning, especially if burned under conditions in which complete combustion did not occur.

"The statistics of the Chief Medical Examiner for Richmond from 1947 to 1951 show a striking decrease in fatal cases of gas poisoning after the substitution was made:

1947—fatal cases of gas poisoning, 13 (suicide, 8; accident, 5).
1948—fatal cases of gas poisoning, 16 (suicide, 9; accident, 6; homicide, 1).
1949—fatal cases of gas poisoning, 9 (suicide, 3; accident, 6).
1950—fatal cases of gas poisoning, 0.
1951—fatal cases of gas poisoning, 0."

I believe that this has been a common experience in many parts of the United States, but have so far been

unable to obtain statistics for any other area than New York.

I was wrong in describing commercial butane as a "natural gas," but it certainly does not, as Mr. Lawrie states, offer the same facilities for suicide as does coal-gas. Dr. Ua Conchubair (December 24, p. 1890) also alleges lethal properties in butane. According to Patty[2] it "causes noticeable drowsiness within 10 minutes at a concentration of 1 per cent. but no other symptoms were observed. . . . Its odor cannot be detected below 0.5% and, judging from the scanty information available, there is little reason to believe that ill-effects would result from the prolonged, repeated inhalation of this amount." With carbon monoxide on the other hand, the prolonged inhalation of concentrations as low as 0.2%, and probably as low as 0.1% in the case of old persons, can be lethal. Patty[2] recommends, as the maximum permissible concentrations for prolonged inhalation, butane 0.37%, carbon monoxide 0.01%. The limit for butane is based upon its inflammability rather than upon its physiological effects.

It is, however, unlikely that butane, whether re-formed or not, will ever be used for public gas supplies other than in a few isolated places like Guernsey, whereas the field for true natural gas, consisting, when not re-formed, almost entirely of methane, is virtually unlimited. The numerous authorities that I have consulted all agree that methane is a simple asphyxiant with no toxic properties, or at worst very slight ones, but acting in high concentrations merely as a mechanical barrier against access of oxygen to the lungs. Mr. Lawrie also stresses the explosive properties of methane and butane when mixed with air. This is, however, true also of carbon monoxide and of coal-gas, though at higher concentrations; in practice almost any prolonged escape of either coal-gas or of natural gas from an open tap will give rise to explosion if a naked light is present in any of the rooms affected, but the danger of death from this cause is very small compared with that of carbon-monoxide poisoning.

Mr. Lawrie also mentions the high cost of converting burners to the use of natural gas, a conversion which has clearly been widespread in America, and thereby stresses my main claim: that a decision ought to be made at a national level as to whether the large saving of lives which would result justifies the expenditure of money which would be necessary. If the initiative in this matter does not come from the authorities directly responsible, then it is the duty of the medical profession to ensure that a decision is not postponed until large amounts of capital have been invested in the re-formation process.—I am, etc.,

London S.W.15. A. E. MOURANT.

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"Glucose-feeder" Syndrome

SIR,—Have any of your readers noted a phenomenon, which I several times observed when practising in a part of the world where food faddism was then rife, and which I used to call the "glucose-feeder" syndrome?

When powdered glucose was first freely upon the market, a notion became widespread among the general public that it must be good for one, and especially for one's children. Many grandmothers bought it for their daughters, who could not afford to buy it for their youngsters themselves. It was in these youngsters, mostly aged about 2 to 7 years, fed liberally on glucose, that I noted what formed quite a syndrome, and most cases could be recognized on sight.

The original complaint by the mother varied: sometimes it was of irritability of temper, sometimes of evanescent rash, sometimes unaccountable rises of temperature, or loss of appetite, or combinations of these. The striking feature of these cases was the "iced wedding cake" look of the child's general appearance, difficult to describe and never noticed by the people living with the patient. Though there was no anaemia or actual oedema, the skin had something of the semi-translucency of the patient with large white kidney. Reducing substance appeared in the urine, but no other abnormality. After hearing the mother's story of the child's illness and noting the peculiar, typical appearance of the child, the question, "He is having plenty of glucose, I expect?" always brought a fervent, "Yes, doctor"; and elimination of glucose from the diet always brought about abatement of the symptoms.

Not so long ago I noted this phenomenon in this country, which prompts me to write this now. This was a child of 12 years of age, whose medical attendant, very experienced and careful, apparently could not account for the peculiar appearance of the child, and ordered a check on the white-cell count as long as the temperature should be inclined to rise. This child had an over-solicitous mother, who, as is always the case in these circumstances, plied the glucose the harder the more the child showed signs of illness. His appearance improved markedly when a more normal diet was instituted.—I am, etc.,

Dumfries. EDNA F. BIRKINSHAW.

Rheumatology and Physical Medicine

SIR,—Professor E. G. L. Bywaters (January 14, p. 120) does himself less than justice as a historian when he belittles the achievements of this country in the field of rheumatology. He must be aware that, as far as the bulk of rheumatic disorders goes, the day-to-day problems of their management are efficiently dealt with in the many departments of physical medicine throughout the country. Nor can he ignore that those in charge of some of these departments have made valuable contributions to the subject. Had Professor Bywaters applied himself to a comparison of physical medicine in the U.S.A. and in this country with the enthusiasm he reserved for postgraduate training, he could not have failed to observe that complete clinical responsibilities—frequently with full in-patient facilities—are assumed in physical medicine departments here, whereas such a situation, if it exists at all, is the exception in the U.S.A. Perhaps the need for so many specialized departments in rheumatology and the expenditure of vast sums of dollars there, as well as the savings to the treasury of the Medical Research Council here, are directly related to this fundamental difference.

While it would be most injudicious to attempt correcting some imperfections by totalitarian interference with the traditional system which has served rheumatology so loyally in the past, no one could reasonably cavil at an increase in the number of centres where research and postgraduate teaching in rheumatology could proceed in a near-academic atmosphere. From

many angles, a graft of the vaunted American system on our existing one with a rapprochement of the medical personnel involved would make for a fruitful and efficient compromise which would not fall far short of the ideal.

If I felt it would make Professor Bywaters any happier, and add to the prestige of rheumatology in Britain, I would gladly initiate a campaign with the object of having every department of physical medicine in this country justifiably renamed Department of Physical Medicine and Rheumatology.—I am, etc.,

St. Thomas' Hospital, London S.E.1. PHILIPPE BAUWENS.

Electrocardiographs in General Practice

SIR,—I have had a direct-writing electrocardiograph in my practice since 1954. It is extremely reliable and very useful in this sparsely-populated rural district 100 miles from the nearest cardiologist. I use it moderately frequently, but not as often as Dr. J. H. B. Urmston and his partner (December 31, p. 1951), and I do not find a tracing can be taken as quickly as he can.

I have found it invaluable because of the speed with which I can have a reasonably reliable diagnosis. I have learnt a lot about reading the tracings by having my diagnoses checked by a cardiologist and by frequent reference to *Clinical Unipolar Electrocardiography* by Lipman and Massie.[1] I now find I rarely require confirmation of my diagnosis, but I still know comparatively little about the positions of the heart, while vector cardiography is a closed book which as yet I have not had the inclination, the necessity, or the time to open.

I am sure many general practitioners would find benefit from the possession of an electrocardiograph, provided they can find the time to take the tracings and to learn to read them, but I do think the benefit will be more to the rural practitioners than to the town men, because the diagnosis can be obtained with an ease and speed which are not otherwise available in the country.—I am, etc.,

Loch Fyne, Argyll. A. C. MAYER.

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Sir James Mackenzie, M.D., 1853-1925

SIR,—It has long been felt by his many admirers, not only in this country but in America and on the Continent, that a new and more exhaustive biography of my uncle should now be written. Professor A. Mair, who holds the James Mackenzie Chair of Social Medicine at St. Andrews University, has been approached and has kindly agreed to do so. Would anyone who may happen to have any letters or private documents (other than books or publications) in any way pertaining to Sir James Mackenzie please communicate direct with Professor Mair, or with myself at University College Hospital?—I am, etc.,

London W.C.1. AMULREE.

Sir Archibald McIndoe

SIR,—I have accepted a commission from his family and executors to undertake the authorized biography of the late Sir Archibald McIndoe, C.B.E., F.R.C.S. I would be most grateful if anyone in possession of personal letters or recollections would communicate with me, c/o Weidenfeld and Nicolson, 20 New Bond Street, London W.1.—I am, etc.,

Pistoia, Italy. LEONARD O. MOSLEY.

Obituary

Sir ALEXANDER INGLEBY-MACKENZIE
K.B.E., C.B., B.M., B.Ch.

Surgeon Vice-Admiral Sir Alexander Ingleby-Mackenzie, a former Medical Director-General of the Navy, died suddenly on January 17 at the age of 68.

Alexander Ingleby-Mackenzie was born on August 19, 1892, the elder and only surviving son of Dr. K. W. Ingleby-Mackenzie, of Ryde, Isle of Wight. He was educated at Repton and Trinity College, Oxford, going on to St. Bartholomew's Hospital for his clinical training. Graduating B.M., B.Ch. in 1916, he entered the Royal Navy as a surgeon lieutenant in the same year. Between 1917 and 1919 he served in H.M. ships *Coledin* and *Cardiff*. In the latter he was in action in the Heligoland Bight in November, 1917, and gave valuable assistance with the treatment of the wounded. His report read, "ability above average," "likely to go far in his profession," and this turned out to be very true. Between the two world wars he held many interesting appointments and specialized in medicine. He twice served at the Royal Naval College, Dartmouth, was on the staff of the Physical and Recreational Training School, Portsmouth, and also Fleet Medical Officer of the East Indies Squadron. He was promoted surgeon lieutenant-commander in 1922, and surgeon commander in 1928.

[Elliott and Fry

In 1935 he retired from the Navy at his own request with the rank of surgeon captain, intending to take up a different career, but he rejoined the service two years later. At the beginning of the second world war he served in H.M. ships *Resolution* and *Royal Sovereign* in the Home Fleet. He then had two years at the Royal Naval Sick Quarters, Dartmouth, before joining the naval hospital ship *Vita* with the acting rank of surgeon captain, made substantive at the end of 1942. In the *Vita* he took part in the landings at Sicily and Italy. Later the ship proceeded to the Far East and he became Fleet Medical Officer, Eastern Fleet. In 1944 he was appointed officer in charge of the medical section of the R.N. Hospital, Haslar, and two years later Principal Medical Officer of R.N. Barracks, Chatham. In December, 1948, he was promoted surgeon rear-admiral and became medical officer in charge of the Royal Naval Hospital, Chatham, Command Medical Officer to Commander-in-Chief, the Nore, and Honorary Physician to the King. He was appointed C.B. and a Commander (Brother) of the Order of St. John of Jerusalem in 1951. In the following year he was made Medical Director-General of the Navy. Knighted in 1953, he was placed on the retired list in 1956, and promoted Knight of the Order of St. John in 1957. After his retirement he became assistant managing director of Arthur Guinness Son and Company Ltd., and was with them until his sudden death.

It was early recognized in the R.N. Medical Branch that Alexander Ingleby-Mackenzie would go a long way, since his outstanding characteristics were his immense enthusiasm and drive, and he never spared himself. He was a first-class games player, had captained the hockey eleven at Oxford, but was almost equally good at golf, tennis, and squash. His appointment to the board of Arthur Guinness showed how highly he was thought of outside the Service. He will be remembered as a very pleasant person who loved both

work and games, and as a very congenial messmate, always willing to give sound advice or a helping hand to all who asked for it.

His death has come as a great shock to all his friends. We extend our deep sympathy to his widow and to his two sons, one of whom is captain of the Hampshire cricket eleven, and daughter.

J. ENGELBRETH-HOLM, M.D.

Professor J. Engelbreth-Holm, professor of pathological anatomy in the University of Copenhagen, died in London on January 17 at the age of 56.

We are indebted to Professor ALEXANDER HADDOW for the following appreciation: His friends and colleagues the world over will have been distressed to learn of the death of Professor Julius Engelbreth-Holm. He was in London to attend a meeting of the Scientific Advisory Committee of the Lady Tata Memorial Trust. In his final illness, great succour was given him by the Middlesex Hospital and the Ciba Foundation. Professor Engelbreth-Holm was born in 1904 in Copenhagen, where his father was a well-known medical practitioner. After graduating M.D. in 1933 (with a thesis on the subject of the avian leukaemias), he worked in the Municipal and Bispebjerg Hospitals, and later became director of the cancer research laboratory of the Danish Cancer Committee (1938–41), and chief prosector of the Finsen Institute and Radium Station of Copenhagen. In 1941 he succeeded Professor Poul Moeller in the chair, and some years afterwards became chief of the Fibiger Laboratory. He was a member of the board of the Danish Medical Society and of the Danish Pathological Society, a member of the Pathological Society of Great Britain and Ireland, and an editor of *Acta pathologica et microbiologica Scandinavica*. At the end of the war and of the German occupation he became a leader (1945–8) in the "medical group of Free Denmark" (*Frit Danmark laegegruppe*). In royal and public recognition he was made a knight of the Order of the Dannebrog.

Engelbreth-Holm's work lay in the fields of experimental pathology, cancer research, and haematology. His main contribution is perhaps his *Spontaneous and Experimental Leukaemia in Animals*, which he was encouraged to write by the Scientific Advisory Committee of the Lady Tata Memorial Trust (under the chairmanship of Sir Henry Dale). Engelbreth-Holm completed the Danish text early in 1940—before the war and ill-health had laid their mark upon him—and entrusted the task of its translation into English (published by Oliver and Boyd in 1942) to Mr. C. L. Heel, formerly of the staff of the British Consulate in Copenhagen. In the preface we read, "It may be suggested that the present time is unpropitious for researches aimed at the saving of life by the conquest of a disease which is relatively rare in man. . . . This very circumstance, however, may have made the year 1940 especially appropriate for taking stock of the existing knowledge of the experimental leukaemias, since it marks the end of a period of intensive research in this field. It is to be hoped, when the present war is over, and it becomes possible for research workers throughout the world to resume their attack on the common enemies of mankind . . . that this book will be found to provide a valuable foundation of collective knowledge, for the better planning of further researches on leukaemia and in neighbouring fields of investigation dealing with such diseases as cancer. . . ." The hope has been abundantly fulfilled. In the years intervening since these lines were written, dramatic strides have been made in our knowledge of the leukaemias and of the leukaemogenic viruses. Engelbreth-Holm's book recorded an essential stage, and for this we must ever be grateful.

He was handsome in presence and a delightful colleague. Especially we admired the fortitude with which he met and opposed the ravages of premature disease. He is survived by his wife Anita, to whom will go the sympathy of his innumerable friends in many lands.

W. S. FENWICK, M.S., F.R.C.S.

Mr. W. S. Fenwick, who retired from the active surgical staff of Charing Cross Hospital in 1922 and became a successful farmer near Salisbury, died in Salisbury Hospital on January 17. He was 79 years of age.

William Stephen Fenwick was born on July 6, 1881. In his youth he developed arthritis of the hip, which necessitated a long rest in the open air, a circumstance which gave him a great interest in and love of the country. He had graduated B.Sc., with honours in botany, before becoming a medical student at Charing Cross Hospital in 1902, and was thus a little older than the average student, but his brilliance soon revealed itself and he took practically all the prizes at the hospital medical school. Qualifying in 1906, he graduated M.B., B.S., with gold medal and honours in surgery, medicine, and pathology, in 1908, took the F.R.C.S. in the same year, and proceeded M.S. (qualifying for the Gold Medal) in 1909. After being a house-surgeon to Sir Herbert Waterhouse he became surgical registrar at Charing Cross Hospital, and on the death of Sir Frederic Wallis he was appointed to the full surgical staff of the hospital—only six years after qualification. Appointments to other hospitals followed in quick succession, and at various times he was on the surgical staff of the Hampstead General Hospital, the Gordon Hospital, the Queen's Hospital for Children, and the Hendon Cottage Hospital.

During the first world war his disability prevented him from joining the Forces, but he did an enormous amount of surgery in the absence of other members of the staff. Unfortunately a motor accident further increased his disability, and this, combined with a "call" to country life, made him decide to retire to south Wiltshire, where he became a well-known farmer. In 1937 he was elected chairman of the south Wiltshire branch of the National Farmers' Union. An excellent fisherman and shot, he led a life well suited to his desires, but during the second world war he undertook work as chairman of the National Service Medical Board in Salisbury.

With his chief, Sir Herbert Waterhouse, Mr. Fenwick wrote a paper on the use of iodine in the preparation of the skin which was largely responsible for its widespread adoption in Britain. He also published a short paper on the use of a sector of small intestine to replace a resected portion of the colon when for certain reasons direct colonic anastomosis proved impossible.

Sympathy is extended to his widow and to his son, Mr. Thomas Fenwick, who, following his father's footsteps, is now consultant surgeon to the Portsmouth group of hospitals.

E. D. D. D. writes: There are very few Charing Cross Hospital contemporaries left to remember that quiet, unobtrusive, but lovable surgeon, Stephen Fenwick. He was lame as the result of an ankylosed tuberculous left hip, but he courageously refused to recognize it as a handicap, though his forced immobilization during his 'teens seriously interfered with his education. He was a brilliant student and qualified in record time—a genius who excelled, without effort, at everything and anything he did.

He was selected unanimously for the post of assistant surgeon to Charing Cross Hospital in 1909. At that time we were both struggling consultants, passing rich on £50 per year as demonstrators of anatomy, but with a bond of true friendship, and a consulting-room in Harley Street which we shared. The long operating sessions at hospital were a great strain on Fenwick's hip, and though he operated sitting on a stool he had to rest his hip at every opportunity. At the end of the first world war his motor-car collided with a tram-car during a black-out. His foot was hard down on the brake pedal, and in consequence his normal right hip took the full force of the impact. He was immobilized for six weeks but returned to work. He realized then that he would have to retire as soon as possible, and in 1922, with his usual courage and enterprise, he bought

a farm at Whiteparish, near Salisbury. He became a very successful farmer with a wide reputation as a reliable veterinary surgeon, but Charing Cross lost a meritorious surgeon and a wise friend.

KARL KLEIST, M.D.

Professor Karl Kleist, professor emeritus of psychiatry in the University of Frankfurt, died suddenly from a myocardial infarction on December 26, 1960. He was 81 years of age.

Karl Kleist was born at Mulhausen, Alsace, on January 31, 1879. He studied in Strasbourg, Heidelberg, Berlin, and in Munich, where he graduated M.D. in 1902. For the next six years he worked in the neurological clinic at Halle, the neurological and psychological institute at Frankfurt-am-Main, and at the anatomical laboratory of the Munich psychiatric clinic. From 1909 to 1916 he was senior physician at the psychiatric clinic in Erlangen, where he became professor in 1915. In the following year he was appointed to the chair of neuropsychiatry at Rostock, leaving there in 1919 to become professor of psychiatry and neurology at Frankfurt and director of the university's neuro- and psycho-pathological research institute. He was a corresponding member or an honorary member of a number of neuropsychiatric and other learned societies in Europe and North and South America, including the Royal Medico-Psychological Association.

H. H. F. writes: Kleist was the last great representative of the German classical neuro-psychiatric era and a past-master of localization of nervous functions, particularly in the brain. For him neuro- and psycho-pathology (whether "organic" or "functional") meant encephalo-pathophysiology. While acknowledging that the parts of the central nervous system work together as a whole, he would stress that this whole is formed by parts of different anatomo-physiological constitutions. He studied neurological and mental diseases by refined techniques of clinical observation and applied the result of his studies for better differential diagnoses of neurological or psychiatric illness, or for the creation of new syndromes. More than 50 years ago he showed that psychomotor disturbances in schizophrenics are of a more organic "senseless" nature than the more "expressive" movements in the more affective (marginal, schizoid, degenerative) psychoses with a better prognosis. He developed tests of speech and intelligence for the finer analysis of schizophrenic symptoms and organic conditions and studied by similar means the different forms of apraxia. He was possibly best known in this country for his work on the constructive and the limb-kinetic apraxias. Kleist was among the first to recognize the importance of the hypothalamus for instinctual disturbances, and emphasized 30 years ago the importance of the limbic system for emotional processes. In 1934 his great work on war injuries of the brain was published; he used later the results of his findings in order to relate the symptoms of the different clinical forms of schizophrenia to disturbances of different functional and anatomical systems in the brain.

When the new neuropsychiatric hospital in Frankfurt was opened in 1930 it contained not only most modern accommodation for the patients, with windows and gardens without bars, but also neurohistological, biochemical, and haematological laboratories and cinematographic, electrophysiological, and neurosurgical units. Kleist was keenly interested in therapy; numerous new drugs were tried out in his hospital, while the value of occupational therapy and rehabilitation of patients was persistently emphasized by him; his hospital was one of the first teaching hospitals in Germany to employ a psychiatric social worker. He was a tireless and passionate worker to the end, and, behind a somewhat rigid, courteous, and dignified surface, a man of great human understanding and generosity, with a dry humour and a combination of boyish curiosity and adult interest in all aspects of life and art. His married life was very happy, for he had found the ideal companion in his wife, who was equally devoted to him and their children.

R. H. V. O. writes: Professor Karl Kleist was not only a remarkable psychiatrist, a great teacher, and a research worker of great keenness and insight, but he was also a man of outstanding personal courage and character. At a visit as recent as the second week of December, 1960, we found Professor Kleist in his Frankfurt research laboratory working as keenly as a young man on the problems of localization of brain function, and later we were given the hospitality of his charming house, where a great amount of his life's work was concentrated. One outstanding monument of his character and integrity, however, is found in his lonely stand in word and print against the intolerance, fear, and ideological nonsense which the former Nazi regime in Germany put against enlightened and humanistic ideas of psychiatry. Anybody who has lived under a totalitarian regime will know the immense danger of exposing himself, and his family too, and the really superhuman courage necessary to make a lone stand against a ruthless mass-machine. Professor Karl Kleist did this, and, side by side with his great contribution to psychiatry, this will be his undoubted claim to our memory.

W. D. FREW, *M.C.*, M.R.C.S., L.R.C.P.

Dr. W. D. Frew, a Fellow of the British Medical Association, died on December 29, 1960, in Kilmarnock Infirmary, the hospital which he had served for many years as a general-practitioner surgeon. He was 79 years of age.

William Douglas Frew was born in Kilmarnock on July 3, 1881, the son of Dr. William Frew. Educated at Spiers School, Ayrshire, Edinburgh University, and the Middlesex Hospital, he first studied dentistry, qualifying L.D.S. R.C.S. in 1905. He then went on to qualify in medicine two years later. After working as house-surgeon to Sir John Bland Sutton at the Middlesex Hospital he returned to Kilmarnock to take up general practice on the death of his father. At the same time he became assistant surgeon at Kilmarnock Infirmary.

Mobilized on August 4, 1914, Dr. Frew served in France throughout the war, winning the *M.C.* in 1918 and being mentioned in dispatches. Returning to his native town in 1919, he remained in general and hospital practice there for the rest of his professional life. A hard-working member of the B.M.A., he was chairman of the Ayrshire Division from 1927 to 1928 and again from 1930 to 1932. A member of the Scottish Committee for many years, he was a member of Council from 1943 to 1946. As a notable mark of the respect they felt for him his colleagues put his name forward in 1959 for inclusion in the Roll of Fellows of the B.M.A.

Dr. Frew was a remarkable personality, devoted throughout his life to the practice of medicine and surgery and an inspiration to the many doctors who looked to him for advice, for friendship, and for encouragement. He will be sadly missed.

B. R. N. writes: It was only during the last twenty years of his life that I had the privilege of knowing Dr. Douglas Frew. A tall gaunt figure, a man of few words but of great underlying charm, he immediately impressed one as a doctor of much integrity and humanity. In his patients, young and old, rich and poor, he inspired confidence and respect. He had a wide and beneficial influence on medical practice in Ayrshire and in the counsels of the British Medical Association. He was a sympathetic guide as well as an example to many of his younger colleagues by reason of the high standards of his practice and his rigid code of ethics. Hard-working and conscientious in the care of his patients, he also spent many hours of his busy day in the surgical work of Kilmarnock Infirmary, and this hospital, as it is to-day, owes much to his unceasing devotion. His skill, wisdom, and clinical acumen were widely recognized by the demands made on him for consultations by his colleagues.

In private life he was happiest living quietly in his own family circle, but he could be the perfect host too—I recall particularly the Christmas dinners which I first attended as

his house-surgeon—and his hospitality was both lavish and sincere; one always felt a welcome guest in his home. On his retirement he went to live in Mauchline, where his books and his garden brought him much peace and contentment. He did, however, suffer a sad blow with the death of his much-loved wife, but for the rest of his life he enjoyed the companionship of his devoted daughter. In spite of physical disability during his last years he continued to take an active interest in affairs in general and all that went on in the medical world in particular. He got great pleasure from the award of the Fellowship of the B.M.A. The end of his last illness came suddenly, but happily not before he was able to have a few hours in the company of his son, who had returned that day from Canada. The great loss suffered by his son and daughter will be shared in some measure by a wide circle of friends and former colleagues.

IAN McCRACKEN, M.B., Ch.B., B.Sc., D.P.H.

Dr. Ian McCracken, who was medical officer of health for County Durham for over twenty years, died at his home at Whitesmocks, near Durham, on January 6. He was 63 years of age.

Ian McCracken was born on October 30, 1897, the son of a minister at Burntisland, Fifeshire. From Whitehill School, Glasgow, he went to Glasgow University, where he graduated B.Sc. in 1921 and M.B., Ch.B. in 1924. Four years later he took the Edinburgh D.P.H. After qualifying he was house-physician and house-surgeon at the Western Infirmary, Glasgow, and then held a number of other hospital posts, at Robroyston Hospital and Sanatorium, East Pilton Hospital, Edinburgh, and Ruchill Sanatorium, Glasgow, before becoming clinical tuberculosis officer in the public health department of Glasgow Corporation in 1931, where subsequently he was a divisional medical officer. In 1937 he was appointed deputy county medical officer for County Durham, succeeding the late Dr. James McIntyre in the senior appointment in the following year. His retirement from the post of county medical officer in 1959 was forced upon him by ill-health. Dr. McCracken was chairman of the Durham Division of the B.M.A. in 1951–2.

G. W. writes: Dr. Ian McCracken's time in office as county medical officer for Durham was a particularly eventful one, with the outbreak of war in the year following his appointment, and then the great changes accompanying the inauguration of the National Health Service. Studious, careful, and thorough by nature, he applied these qualities to great effect in carrying out the onerous duties of his post. His decisions were given only after consideration of all the particular factors involved—factors which his orderly methods of thought enabled him to grasp and assess with sure judgment. In debate he preferred to await a request for his opinion, and when that came, as it surely would, his views were given clearly and with a characteristic economy of words. Essentially he was a scholar, Greek (he read from the original) and mathematics being among his recreations, and he used time free to him in his retirement to study the Russian language. While these features give a guide to his character those who knew him will remember most his ready sympathy and interest and above all his complete integrity and sense of purpose. They sympathize deeply with his wife in her loss.

Dr. A. K. MACRAE writes: Those of us who were privileged to have been the friends of Ian McCracken at Whitehill School and at Glasgow University remember him as a really outstanding personality. Intellectually he was on a plane above most, being a brilliant mathematician and student of the classics. Throughout his many scholastic successes he remained modest and unassuming, and this may have been one of the reasons for his popularity with us all. On first acquaintance his manner was reserved, but, with greater intimacy, this reserve readily broke down to reveal a pretty wit, a keen sense of humour, and a refreshing vivacity. Our various professional activities did not allow of our spending much time together in later years, but there were few with whom one could spend an evening as pleasantly as with Ian McCracken. As host or guest he was thoughtful, courteous, and considerate. It was obvious that those who had worked with him over the past twenty-one years in Durham held him in high regard, conscious of his erudition and culture and admiring his loyalty and integrity. He bore his long illness with courage and patience, nursed by his wife, Grace, to whom goes our deep sympathy.

W. N. STIRLING, L.R.C.P.&S.Ed.

Dr. W. N. Stirling, who was for many years principal medical officer of the Balisera district of East Pakistan, died at his home at Helensburgh, Dunbartonshire, on November 8, 1960.

William Neilson Stirling was born at Rutherglen, Lanarkshire, the son of the Rev. William Stirling, and was educated at Hutchesons' Grammar School there. He studied medicine at the Anderson College, Glasgow, and at the university, taking the Scottish triple qualification in 1923. He then held an appointment as a ship surgeon before becoming medical officer on a tea estate in Northern Bengal. From 1926 to 1928 he was medical officer to mission hospitals in East Africa, leaving there to take up the post of district medical officer at Kalighat, in the province of Sylhet, Assam. A few years later he was appointed principal medical officer of the Balisera district, in what is now East Pakistan. He retired from this appointment in 1954 and returned to Scotland, subsequently giving occasional assistance to medical officers of mental hospitals. A member of the British Medical Association for nearly 40 years, he was three times chairman of the Surma Valley Division and its honorary secretary in 1941–2. He was also president of the Assam and North Bengal Branch in 1943–4. He leaves a widow, a son, and a daughter.

C. S. P. H. writes: William Neilson Stirling was one of those great souls whose life was dedicated to his profession. Before taking up his appointment as medical officer in charge of the Balisera Medical Association, he worked in an isolated mission field in East Africa. There he learned the hard way of living, and studied tropical medicine amid surroundings where this specialty was indeed in its infancy. Little was known about the many indigenous diseases, and in consequence a great deal of hard work came his way. He treated his patients with whatever was available, and tried to prevent the spread of disease by the then well-known but not very effective methods at his disposal. When he took over the work in Balisera he met the late Dr. G. C. Ramsay, and collaborated with him in carrying out a tremendous antimalarial scheme. At that time the vector *Anopheles minimus* was the scourge of the countryside. Dr. Ramsay promoted a comprehensive anti-larval scheme, shading all drains and waterways, and silting up low-lying river beds and bogland. Stirling planted an enormous number of plants to provide shade, and at one time throughout his tea estates his shade programme covered a distance of 100 miles. In addition to the anti-larval control work Stirling opened a well-equipped laboratory and trained both technicians and antimalarial field workers.

During the second world war he shouldered enormous responsibilities, not only in his own practice but in other neighbouring areas. Balisera Valley is situated along the main line of the Assam and Bengal Railway, which fed the Assam–Burma front, and Stirling had many extra duties to carry out in connexion with Royal Air Force and military camps. He was a quiet, very calm individual who never became ruffled, and was invariably kind and considerate to all alike, from the humblest coolie to the very worried estate manager and his family. Everyone respected him and recognized his great worth.

D. ST. CLAIR MACKENZIE, M.B., B.Ch.

Dr. D. St. Clair Mackenzie, who was in general practice at Kew Gardens, Surrey, died on December 17, 1960. He was 58 years of age.

Derek St. Clair Mackenzie was born on June 10, 1902. He studied medicine at Trinity College, Dublin, representing his university in cross-country running. After graduating M.B., B.Ch. in 1926, he entered general practice two years later at Wantage, Berkshire, where he became also surgeon to the cottage hospital and a medical officer under the Wantage Union. In 1938 he went into partnership with Dr. G. J. Maguire at Kew Gardens. After serving as a captain in the R.A.M.C. throughout the second world war, he returned to Kew Gardens to carry on the practice alone, Dr. Maguire having died in 1941. For many years he served on the executive committee of the Richmond Division of the B.M.A., being chairman of the Division in 1952–3.

N. M. C. writes: Dr. D. St. Clair Mackenzie, who died after a protracted illness, will be remembered with affection, not only by his patients but also by his professional friends. Having been associated with him for some years, I feel able fully to appreciate his well-deserved success. His kindness to his patients and his understanding of their problems helped him in no small measure to build up a large practice. He was indeed greatly liked by all who sought his help and for whom he worked so hard.

DOROTHY HOPKINSON, M.B., B.S.

Dr. Dorothy Hopkinson, who practised in Gosforth, Newcastle upon Tyne, and was formerly anaesthetist to the Royal Victoria Infirmary, died on December 21 in Newcastle General Hospital.

Dorothy Hopkinson was born at Monkwearmouth, County Durham, the eldest of five children, and only daughter, of Canon Hopkinson. Educated at Roedean, she did not immediately become a medical student, and during the first world war she worked as a factory inspector. She then finally decided to become a doctor and enrolled as a medical student at the College of Medicine of the University of Durham. Graduating M.B., B.S. in 1926, she held the posts of house-surgeon and assistant resident anaesthetist at the Royal Victoria Infirmary and assistant resident medical officer at the Clapham Maternity Hospital. Thereafter she went into practice in Newcastle, where she spent the remainder of her life.

E. W. O. writes: By the death of Dorothy Hopkinson, Newcastle upon Tyne has been bereft of a rare personality and of a doctor greatly beloved by her patients. From the outset of her career she built up a very personal private practice. Her patients had the greatest affection for her. For some years she was on the staff at the Royal Victoria Infirmary as an anaesthetist, but her heart was in general practice and she eventually gave up anaesthesia.

Apart from medicine, her interests were in music, gardening, reading, and walking. One met her at most concerts, blissfully absorbing the music of the masters. She was a zealous gardener and had the greenest of green fingers: her garden was always a joy to behold. In wartime, flowers and vegetables were intimately mixed, with cunning and success: when one visited her, one always came away with a bunch of flowers and a salad. She loved the open moors of Northumberland and Durham and in the old days tramped many a happy mile over them. She had an eye, too, for old furniture, and in her own home cherished it lovingly—in fact, she was houseproud.

There was more than a streak of the dreamer in Dorothy Hopkinson. She was a rather detached and reserved person and took knowing, but, when really known, was whimsical and delightful. She gave up practice quite recently and survived her retirement by only a matter of weeks. She had a short illness and was buried at Whitburn, where her father had been rector and where she spent many of her earlier days.

H. K. HANDOO, M.B., B.S.

Dr. H. K. Handoo, who was in practice in north-west London, died at his daughter's home in Calcutta on December 26, 1960. He was 60 years of age.

Hari Krishna Handoo studied medicine at Lucknow, graduating M.B., B.S. in 1926. Early in his career he joined the Indian Medical Service and served with the Indian Army for many years. During much of his distinguished medical career at this stage he was stationed on the North-West Frontier, and he could tell many exciting tales of this eternally turbulent region. He served also with the Forces in Shanghai. He retired from the I.M.S. with the rank of captain in 1935, and went into practice in Tufnell Park, in north-west London.

D. A. P. writes: Dr. H. K. Handoo, who died after a trying illness borne with characteristic courage, was very well known in medical and Indian circles in London. When he entered general practice he soon acquired a reputation as an uncommonly good diagnostician and an unusually sympathetic doctor. His substantial practice he carried on with the aid of a partner. To the exacting burdens of a busy medical life he cheerfully and generously added the onerous duties associated with the administration of several Indian social and political associations, at the meetings of which he was always a popular figure. He saw the last war through, from start to finish, in active practice in Tufnell Park. There must be many to-day in that area of London who could testify to the help they received from him whether at his surgery, in their homes, or in public shelters. He was well known, too, in the world of sport. Himself in his younger days an All-India athlete, he was always ready to encourage with expert advice young Indians who aspired to world honours in sport. India was fortunate indeed to have him as her representative in the International Tennis Federation.

Dr. Handoo leaves a widow and daughter.

J. A. HISLOP, M.D., D.P.H.

Dr. J. A. Hislop, formerly medical officer of health for the county borough of Tynemouth, died at his home at Hartsop, Westmorland, on December 31, 1960. He was 95 years of age.

James Andrew Hislop was born at Birkenhead on May 17, 1865, the son of William Hislop, an engineer, who superintended the building of the first ship for use on Lake Titicaca, 12,500 ft. above sea level, on the border of Bolivia and Peru. James Hislop lost both parents while he was still a boy, and was brought up by his uncle, the Rev. David Hislop, of Hawick, Roxburghshire, where he attended the Teviot Grove Academy. After leaving school he studied pharmacy, qualifying at the age of 22. While working with a firm of chemists in Belfast he undertook night duty, and this enabled him to study medicine at the old Queen's College, Belfast. As a medical student he gained a number of prizes, including the Malcolm exhibition and a gold medal in diseases of children. After obtaining the Scottish triple qualification in 1893, he was in private practice for a time and then spent three years in India. Having taken the Brussels M.D. in 1903, and the D.P.H. of the Scottish Royal Colleges in 1904, he became assistant medical officer of health for Lanarkshire, and from 1909 to 1930 was medical officer of health for Tynemouth. A member of the British Medical Association for nearly 66 years, he was honorary secretary of the Tynemouth Division from 1922 to 1929, and he was also president of the Northern branch of the Society of Medical Officers of Health for two consecutive years. On his retirement he was made a life member of the society. While at Tynemouth he did much to improve the tuberculosis

and maternity and child welfare services, persuading the council to provide a maternity home in the borough. When he retired from public-health work he received presentations not only from the health committee and the county borough council of Tynemouth but also from the medical practitioners of the area, with whom he had always worked in close co-operation. It was natural that he should go to the Lake district on his retirement, for he had spent his holidays there almost yearly for over 30 years. He had become interested in the recording of earthquakes when in India, and in his new home at Hartsop, in Patterdale, he installed a seismograph—one of the few in private ownership in Britain.

Dr. Hislop was a widower without family.

R. L. GALLOWAY, M.B., Ch.B., F.R.C.S.Ed.

The obituary of Mr. R. L. Galloway was published in the *Journal* of December 24 (p. 1890).

An old colleague writes: There can have been few British surgeons in the second quarter of this century who crowded so much work into their life as R. L. G. At the North Middlesex and later at Chase Farm he got through an incredible volume of general surgery, with great skill, speed, and gusto. In the 'thirties at the North Middlesex it was nothing for "Robbie" to finish a list of ten cases by lunch-time and on a busy take-in to operate on another dozen emergencies, finishing his day at 3 a.m. by giving a lift home to the no-longer anxious relatives of his last case. He then drove on to his own bed. These emergencies would be of all sorts—provided they were surgical, it didn't matter—appendices, obstructions, fractures, mastoids, head injuries—Robbie took them all in his stride, deftly, quickly, with no movement wasted. He loved his work and his patients. He never grumbled at there being too much to do: but he was the first to admit that he would have liked more time and facilities to collect and consider his work—provided there was no fall off in the amount. He was so busy *doing* that he had no time and little use for writing. He might well have inspired Bernard Shaw to say, "He who can, does: he who cannot, teaches." Curiously enough, however, on the two or three occasions when he was persuaded to report his surgical experiences before the Section of Surgery of the Royal Society of Medicine or the Middlesex Medical Society, his contributions were notably good. His papers on perforated peptic ulcers and on thymectomy for myasthenia gravis come easily to mind, though he himself regarded them almost as a penance. At two points in his life he took over administrative control of a hospital: of Chase Farm to get it going for E.M.S. purposes, and of the West Middlesex to prepare it for the developments of the post-war period. His old friends regarded the latter move as typical of Galloway's altruism. Anyhow, it was a move which brought him a certain amount of frustration; and in the last few years he had to face the tragedy of Parkinsonism and of his surgeon's hands losing their cunning.

Robbie looked every inch a surgeon, doing his rounds in his bespoke white coat with button-up collar—perhaps his only foible apart from fast cars and home-made motor-bikes. For years he spent his summer holidays driving his motor-bike as far as he could to some wild corner of Europe, and back home again in a fortnight. The sympathy of thousands of his old patients and friends goes out to his wife, son, and daughter.

D. A. C. R. writes: As a result of the evacuation of the London teaching hospitals early in the second world war, I found myself, together with my fellow students from the London Hospital, established at Chase Farm Hospital, Enfield, during the blitz of 1940. It was not long before we realized our great fortune in thus coming under the influence of the medical superintendent, Mr. R. L. Galloway—"the Boss" as he became affectionately known to us all. My earliest clinical memories were of rounds on his wards. One was immediately struck by his genuine care for patients as individuals—whether it was the badly burned Cockney fireman from the London bombing or the wounded Army captain flown back from North Africa. All alike received his individual care and attention. His quiet and relaxed relationship with his patients—as often as not he would call them by their Christian names—unfailingly won their confidence, respect, and admiration.

Not only did he administer the running of the hospital and undertake a large part of the surgery, but he also took upon himself the responsibility for teaching the students. While not a born lecturer, he had a knack of sustaining our interest by punctuating his lectures with amusing anecdotes and accounts of some hair-raising experience of his earlier career. It was at the bedside, however, and in the operating theatre that Mr. Galloway was at his brilliant best. His assessment and diagnosis of the acute abdomen were quite outstanding, while to see him tackle such a case in the operating theatre was a revelation of surgical exposition which could not have been bettered. His technique was quite superb, embodying such classical qualities of gentle though deliberate handling of tissues, economy of movement, and a purposefulness which gave the whole performance an unhurried appearance, though in actual fact he was an extremely rapid operator. It was a delight to work with such a man, as I learned subsequently on becoming his house-surgeon. There are many who will recall those wartime days at an E.M.S. hospital when a fine spirit of comradeship and endeavour pervaded its every department and activity. That was undoubtedly due largely to the personality of its superintendent. It was indeed a privilege to have worked with Mr. Galloway, and I treasure many happy memories of an association over the years with him and his delightful family.

Medico-Legal

BARRIER CREAMS

[FROM OUR LEGAL CORRESPONDENT]

Dr. F. Ray Bettley recently expressed (*British Medical Journal*, November 19, 1960, p. 1467) his views on the efficacy of barrier creams in preventing dermatitis. In a personal injuries action heard subsequently in the High Court, those views were put before the Court in a letter which, said Mr. Justice Edmund Davies, "reflected a state of affairs which ought to receive attention in some quarters" (*The Times*, January 18).

The action, which failed, was brought by a machine-tool fitter against his employers, a firm of concrete manufacturers, on the grounds that he had contracted dermatitis through their negligent failure to provide barrier cream for his use when working with his hands in contact with cement, grease, and dirt.

Among the defences pleaded by the employers was the allegation that barrier cream would not have prevented dermatitis, and therefore it could not be negligent to fail to provide it. Mr. Justice Davies, in giving judgment, said that on the evidence he was inclined to the view that the plaintiff had suffered not from contact dermatitis but constitutional eczema. That was sufficient to decide the case, but, in addition, he was by no means satisfied that barrier cream would have prevented the dermatitis, even if it had been contact dermatitis. On this point he had heard medical evidence, and had also read Dr. Bettley's letter. It was Dr. Bettley's view that a workman's condition might even be worsened by using barrier cream. *The Times* reported Mr. Justice Davies as summarizing Dr. Bettley's letter as follows:

> "Dr. Bettley's letter was to the effect that the principle or theory of barrier cream was a good one—i.e., it was supposed to provide an invisible layer on the skin which prevented noxious substances reaching the skin. He added that, because of its theoretical advantages, doctors had often been forced to

admit that barrier creams might do good and could not do harm, and in that way its provision had been given an exaggerated importance, especially in the courts. He continued that the only proof of the value of barrier cream must come from properly conducted trials carried out under industrial conditions and followed eventually by an assessment of the incidence of dermatitis, and said that good evidence of this kind of the value of barrier creams had seldom or never been produced and that their value was still based upon theory and upon the specious claims of those who manufactured and sold them. He summed up the position by saying that the practical value of a barrier cream in preventing dermatitis due to cement or oil had not been proved by scientific evidence and was a matter only of presumption, and added that there were some, both dermatologists and industrial officers, who considered that barrier creams did more harm than good."

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

The Raymond Horton-Smith Prize for 1959–60 has been awarded to Dr. A. M. Barrett.

UNIVERSITY OF LONDON

The title of Reader in Medicine in the University has been conferred on Dr. P. H. Sanderson in respect of his post at St. Mary's Hospital Medical School.

UNIVERSITY OF WALES

In Congregation on December 19, 1960, the following degrees were conferred:

M.B., B.CH.—Elizabeth R. M. Archer, P. G. Cunningham-Davis, D. G. Daniels, B. E. Deere, M. D. Edwards, J. N. P. Hughes, R. H. Hughes, C. D. Isaacs, K. Jayasinghe, Marlene M. Jones, T. T. Jones, Margaret M. L. Lord, S. N. Nirsimloo, M. J. C. Povey, B. A. Stratford, A. C. Williams.

WELSH NATIONAL SCHOOL OF MEDICINE

At a Congregation held on December 17, 1960, the following degrees were conferred:

M.D.—C. P. Seager.
M.CH.—G. E. Heard (with distinction).

QUEEN'S UNIVERSITY OF BELFAST

At a Graduation ceremony on December 20, 1960, the following degrees were conferred:

M.D.—D. A. Blair, D. McC. Boyle, W. E. Glover, C. A. J. Macafee, E. S. Mitchell, Betty Nicholl, S. D. Roberts, J. Willis.
M.B., B.CH., B.A.O.—C. M. Craythorne, A. P. F. Frank, W. H. K. Haslett, John Joon Hai Ho, D. W. Hunter, Barbara E. A. McMaster, M. R. O'Neill, R. H. Rickaby, Maureen E. A. Thompson.

UNIVERSITY OF BRISTOL

The following candidates have been approved at the examination indicated:

FINAL M.B., CH.B.—L. M. Ajabor, Frances N. Burton, Belinda R. Davies, W. O. Gbajumo, D. D. Kennedy, W. T. Morris, J. J. Nicholas, G. H. Robb, H. Ruhomaully, R. M. Sykes.

SOCIETY OF APOTHECARIES OF LONDON

The following candidates, having completed the final examination, have been granted the diploma of L.M.S.S.A.:

J. J. Aitken, W. K. Blenkinsopp, J. Brown, M. H. Chu, R. N. Drepaul, H. M. Gillespie, F. D. Habib, C. S. Jayakumar, J. M. Lilwall, R. Marris, B. R. Middleton, G. Z. Shenouda, P. Singh, I. G. Strang, J. Swallow, A. Thomas, I. A. Tuncer, C. R. S. M. Wynne-Roberts.

The following candidates have been awarded the diploma of Mastery of Midwifery: R. M. Burton, F. L. W. Collings.

Vital Statistics

Influenza

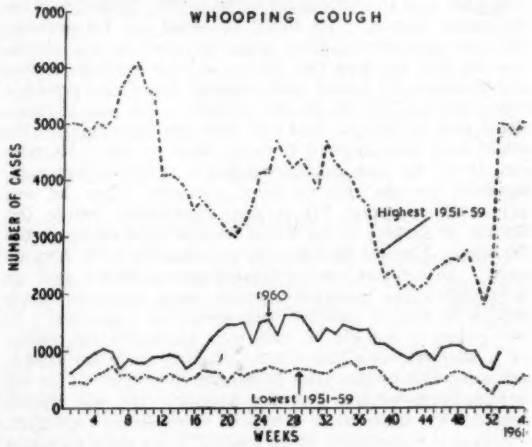
At the end of last week influenza was still prevalent in the Midlands and in parts of the North-western Region. Influenza virus A had been isolated from a number of cases in the Midlands. In England and Wales generally new claims to sickness benefit increased by about 8% and were relatively high in the Midlands and North-west. During the week ending January 14 there were 246 deaths from influenza (150 in the previous week) in England and Wales: most of them occurred in the areas where influenza was prevalent and were restricted almost entirely to middle-aged or elderly persons. There was little change in the number of deaths from pneumonia (1,149) and a slight rise in the deaths from bronchitis (1,371), though both figures were substantially higher than in the same week last year. During the week ending January 10 applications (1,490) to the Emergency Bed Service for London fell a little compared with the previous week, but were about 300 more than in the corresponding week last year.

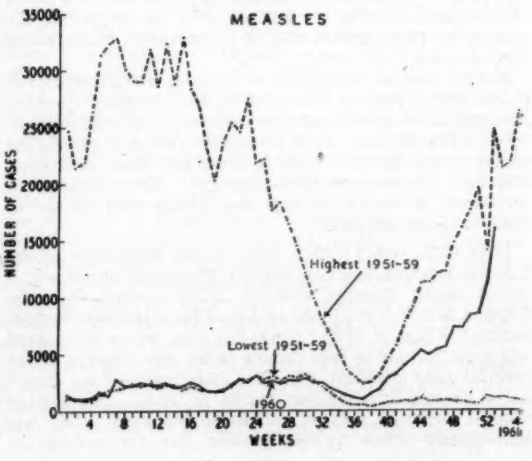
Births and Deaths in 1960

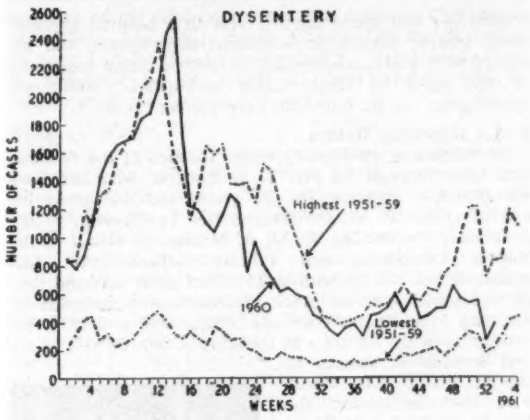
Live births registered in England and Wales in 1960 (according to provisional figures given by the Registrar-General) amounted to 782,673—32,290 more than in 1959 and the highest figure since 1947. The rate per 1,000 population was 17.1, the highest rate since 1948. Deaths numbered 526,278, giving a rate of 11.5 per 1,000 population (11.6 in 1959). The death rate of infants under 1 year of age fell to the low figure of 21.7 per 1,000 live births (22.2 in 1959 and 29.6 in 1950). The stillbirth rate was also low—19.7 per 1,000 live and stillbirths (21 in 1959 and 22.7 in 1950).

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960–1 thus ———. Except for the curves showing notifications in 1960–1, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available

	Week Ending Jan. 7	Jan. 14
Dysentery		
Oxfordshire	2	**41**
Bullington R.D.	0	**38**
Yorkshire West Riding	87	**81**
Leeds C.B.	26	**23**
Measles		
Bedford	254	**350**
Luton M.B.	73	**130**
Durham	547	**675**
South Shields C.B.	84	**102**
Sunderland C.B.	93	**107**
Essex	691	**624**
Harlow U.D.	174	**178**
Lancashire	2,676	**2,047**
Bolton C.B.	204	**202**
Liverpool C.B.	283	**255**
Manchester C.B.	330	**234**
London	1,390	**1,310**
Camberwell	149	**124**
Islington	185	**132**
Paddington	62	**103**
Middlesex	451	**468**
Willesden M.B.	125	**161**
Nottinghamshire	717	**508**
Nottingham C.B.	174	**137**
Oxfordshire	254	**241**
Oxford C.B.	216	**191**
Peterborough, Soke of	158	**108**
Peterborough M.B.	154	**104**
Suffolk	393	**268**
Ipswich C.B.	268	**104**
Warwickshire	642	**604**
Birmingham C.B.	449	**298**
Coventry C.B.	122	**177**
Yorkshire East Riding	182	**159**
Kingston upon Hull C.B.	151	**118**
Yorkshire West Riding	1,331	**1,046**
Bradford C.B.	153	**153**
Leeds C.B.	278	**176**
Glamorganshire	718	**606**
Swansea C.B.	308	**193**
Diphtheria		
London	3	**3**
Camberwell	3	**2**
Warwickshire	1	**2**
Birmingham C.B.	1	**2**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 7** (No. 1) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	4	3	5	0	1	5	0	2	0	4
Dysentery	389	33	105	19	4	840	174	211	6	9
Encephalitis, acute	2	0		0		3	1		0	
Enteric fever:										
Typhoid	0	0	0	0		2	1	1	0	1
Paratyphoid	4	0	0	0		7	0	0	0	1 (B)
Food-poisoning	93	22	12	2		134	24	29	0	
Infective enteritis or diarrhoea under 2 years				17	28				14	22
Measles*	15,989	1390	197	194	276	1,407	17	26	16	7
Meningococcal infection	26	1	10	2		19	4	11	0	1
Ophthalmia neonatorum	13	2	2	0		16	2	5	0	
Pneumonia†	742	45	389	12	11	420	21	307	2	9
Poliomyelitis, acute:										
Paralytic	2	1	0	} 0		{ 2	0	0	} 0	
Non-paralytic	0	0	2			2	1	0		
Puerperal fever§	157	27	9	0		189	26	9	1	
Scarlet fever	416	31	52	24	18	800	38	145	24	21
Tuberculosis:										
Respiratory	301	40	31	7		397	51	53	16	
Non-respiratory	35	3	6	5		54	2	6	5	
Whooping-cough	968	54	68	11	43	667	74	121	11	79

DEATHS	1961 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	1	3	0	0	8	0	1	0	0
Influenza	150	5	1	0	1	34	2	4	0	1
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	1,143	80	33	23	13	614	47	21	11	10
Poliomyelitis, acute	0	0		0	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 103	{ 9	} 14	{ 2	6	} 79	{ 0	8	1	5
Non-respiratory		0		1	0		1	0	0	1
Whooping-cough	2	0	1	0	0	0	0	0	0	1
Deaths 0–1 year	395	52	37	8	21	325	46	22	9	12
Deaths (excluding stillbirths)	14,277	1163	795	196	267	10,908	848	730	173	184
LIVE BIRTHS	16,438	1433	1011	327	353	15,587	1288	1312	266	329
STILLBIRTHS	291	29	15			289	19	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Include primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Plans for Edinburgh Royal Infirmary

A scheme for rebuilding the Royal Infirmary, Edinburgh, without interfering with its smooth running has been outlined by Professor ROBERT MATTHEW, professor of architecture at Edinburgh University. Professor LLEWELYN DAVIES, professor of architecture at London University, co-operated in preparing the plans. These envisage a teaching hospital of 800 beds—a reduction of 300 on the present figure—costing between £7m. and £9m. and taking six years to build.

The scheme suggests that five central buildings, including a nurses' home, should be demolished first, that a boiler-house should then be built, followed by a 12-story ward block, facing across the meadows, and the teaching buildings, and that the demolition of the old hospital could then proceed. In addition, there would be garage space for 600 cars, a tunnel linked with the University buildings in George Square, and space for the Sick Children's Hospital to be built at a later date. The Florence Nightingale Nurses' Home and the Simpson Memorial Maternity Pavilion would be retained. A detailed programme has still to be worked out.

H.M. Senior Medical Inspector of Factories

Professor T. A. LLOYD-DAVIES, whose appointment to succeed Dr. SYBIL HORNER as H.M. Senior Medical Inspector of Factories was noted in last week's *Journal*, was born in 1909 and educated at Woking Grammar School and St. Thomas's Hospital, where he was awarded the Mead Medal (medicine and pathology) and the Toller and Wainwright Prize (medicine). He qualified M.R.C.S.Eng., L.R.C.P.Lond., and M.B., B.S.Lond. (gold medal) in 1932, M.R.C.P.Lond. in 1933, proceeded M.D.Lond. in 1934, and was elected F.R.C.P. Lond. in 1952.

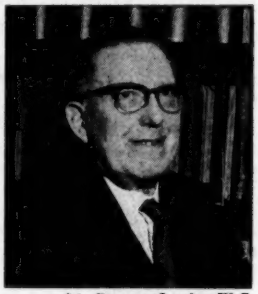
In 1933 he was appointed house-physician at St. Thomas's to Sir MAURICE CASSIDY, and medical registrar to Sir HENRY TIDY, becoming resident physician there in 1935. In 1934 he was captain, R.A.M.C.(T.), and was mobilized at the outbreak of war, being directed to return to civilian work in 1940. He went to Boots Pure Drug Company, Ltd., Nottingham, as medical officer in 1936, was appointed factory doctor in 1942, and became the company's chief medical officer in 1946. He joined the University of Malaya to take up his present post as professor of social medicine and public health in 1953. He was a member of the Industrial Health Services Committee (Dale Committee) in 1951, and has served on many others. He is widely travelled and has studied convulsive therapy in Holland, Belgium, and Switzerland; the design of hospitals in Belgium and Holland; infertility among the Muruts in British North Borneo, at the invitation of the government there; and the Flying Doctor Service in Australia. He was awarded a Rockefeller Travelling Fellowship in 1957 to visit the U.S.A., Canada, Fiji, and Australia to study the teaching of preventive medicine. His publications include articles on medicine, pulmonary disease, industrial and social medicine, old persons, adolescents, and health education.

General Practice Training Appointments

The British Postgraduate Medical Federation is once again offering two-year rotating appointments to those who wish to train for general practice. The Nuffield Provincial Hospitals Trust is giving financial aid, and the Nuffield practitioner will spend his first year in a hospital appointment, gaining experience in special departments, and his second with a general-practitioner trainer, seeing something of the work of local health authorities. Additional information can be found on advertisement p. 43.

B.M.A. Librarian Retires

At its meeting on January 18 the Council of the Association bade farewell to Mr. T. J. SHIELDS, who has been the B.M.A.'s librarian for 32 years, and welcomed his successor, Mr. F. M. SUTHERLAND (see *Supplement*, p. 22). A few days before Mr. A. M. A. MOORE, on behalf of the Science Committee and Library Subcommittee, had presented Mr. Shields with an inscribed silver inkstand, and on the same occasion other presentations were made to Mr. and Mrs. Shields from the official staff and from his colleagues in the library. In speaking of Mr. Shields's long and invaluable services to the Association, Mr. Moore said that he joined the library staff of the Royal Society of Medicine in 1913, that he served in the Army during the first world war and won the Military Medal, and that he became librarian of the B.M.A. in 1929, succeeding the late Mr. Spencer Honeyman, who had been in charge of the library since it was first founded in 1888. During Mr. Shields's term of office the library had moved, first from the present Hastings Room to what are now Committee Rooms C and D, and later to the Garden Court Wing, where further expansion is in progress. The number of readers who visited the library or borrowed books in 1960 was 38,000; 32,000 books were borrowed and 12,000 parcels of books were posted. Mr. Moore concluded by saying that he personally had always received the most ready and efficient help from Mr. Shields in the preparation of papers and so on, and he was sure that every other member who used the library would say the same and would wish to add their good wishes to all those which Mr. and Mrs. Shields would be receiving.



[A. Dawson, London W.C.

Mr. F. M. Sutherland, who succeeds Mr. Shields on February 1, was born in 1921. After taking a degree in history at Cambridge, where he was at Queen's College, he took the University of London's diploma in librarianship and became a Fellow of the Library Association. He has held the posts of senior assistant in the library of the London School of Hygiene and Tropical Medicine and sub-librarian of the Wellcome Historical Medical Library.

Lady Tata Memorial Trust

The Trustees of the Lady Tata Memorial Trust invite applications for grants, scholarships, and fellowships for research on diseases of the blood, with special reference to leukaemia, in the academic year beginning October 1. In view of the affinity between leukaemia and other forms of neoplastic disease, candidates with programmes of research on any aspect of malignant disease which may throw light on problems of leukaemia will be eligible for consideration. The Trustees specially wish to encourage studies of the leukaemogenic viruses in mammals, the epidemiology and natural history of leukaemia, and the genetical and cytological aspects. Scholarships at the rate of £800 sterling a year for whole-time research, with proportional adjustment for work on a part-time basis, are awarded for the personal remuneration of workers carrying out approved research under suitable direction. The Trustees may award one or more Lady Tata Fellowships at the rate of £1,200 a year to senior workers with research experience. Grants of variable amount are made for research expenses, or to provide scientific or technical assistance for senior workers. Details and application forms may be obtained from the

Secretary of the (European) Scientific Advisory Committee, Lady Tata Memorial Trust, Chester Beatty Research Institute, Fulham Road, London S.W.3. Applications must be submitted before March 31, and awards will be announced by the Trustees in June.

Meals on Wheels

A survey of the meals-on-wheels services in Great Britain has been made by the Government Social Survey (Central Office of Information). The survey was initiated and financed by the National Corporation for Old People. Mr. G. C. GIBBS, chairman of the corporation, concludes that "the scale on which this service should be provided to meet all needs is beyond the scope of the voluntary finances and their resources of manpower, and it is clear that the time has come when local authorities, in spite of the ever-increasing demands on them, should become responsible for this important service. At the time of the survey 20,595 people were being served with an average of 1.93 meals a week, and the survey estimates that the number of recipients could be almost doubled and the number of meals served more than quadrupled. The report is available from the National Corporation for Old People in two forms: original version, *Meals on Wheels for Old People*, price 7s. 6d.; shortened version, *Outlines of a Survey on the Meals on Wheels Service*, price 2s. 6d.

Papworth Village Settlement

The Papworth Village Settlement, which is no longer restricted to those suffering from tuberculosis, has extended its existing scheme for handicapped persons. Men and women who are not able to reach the required standard for the Ministry of Labour training scheme may now be admitted for permanent residence and sheltered occupation in the Settlement's new workshop. Men and women up to the age of 45 (and older in exceptional circumstances) can be considered for admission. Full details of the scheme can be obtained from the Secretary, Papworth Hall, Papworth Village Settlement, Cambridge, to whom applications should also be sent.

Additions to B.M.A. Film Library

Copies of the following films have been presented to the B.M.A. Film Library by Ciba Laboratories, Ltd., *Medical World*, and A. Wander, Ltd.:

Physical Diagnosis: The Ear and Hearing. 16mm. colour, sound, 28 min., 1960, U.S.A.* *Physical Diagnosis: Larynx.* 16mm. colour, sound, 12 min., 1960, U.S.A.† *Appointment Systems in General Practice.* 16mm. black-and-white, sound, 26 min., 1960.* *100 Million Electron Volts Against Cancer.* 16mm. black-and-white, sound, 45 min., 1960, Swiss.† (*Suitable for undergraduate and postgraduate audiences. †Suitable for undergraduate, postgraduate, specialist, and consultant audiences.)

British National Committee for the History of Science

The Royal Society has formed a British National Committee for the History of Science, under the chairmanship of Sir HAROLD HARTLEY. Medicine is to be represented by the Faculty of the History of Medicine and Pharmacy of the Worshipful Society of Apothecaries.

Experimental Animals in U.S.A.

A Bill to provide for the humane treatment of experimental animals in the United States of America will be reintroduced when Congress reassembles. It provides for the setting up of a licensing system under the direction of the Ministry of Health, Education, and Welfare, for inspection, and for rules concerning the accommodation and husbandry of the animals, limitation of the infliction of pain, and the keeping of records. (*Annual Report to 30th June, 1960*, Universities Federation for Animal Welfare.)

Grants, Gifts, and Bequests

A candlestick bearing the mark of Matthew Boulton (*circa* 1750/60–1840) has been given to the faculty of medicine of Birmingham University by Professor C. F. V. SMOUT.

Birmingham University has accepted the renewal of a grant of $25,000 from the Population Council, Inc., to the department of anatomy for ovarian studies, and a grant of £36,000 for a five-year period from the Nuffield Foundation to the department of medical biochemistry and pharmacology for research on the biological effects of oxidized fats.

A grant of £25,000, spread over five years, has been made to the University of Oxford by the United States Public Health Service to enable a survey into the causes of cancer and leukaemia to be extended. The survey is being carried out under the direction of Dr. ALICE STEWART, reader in social medicine at the university.

In Brief

It is hoped that Ceylon's second medical college will be established in temporary buildings at Peradeniya in July this year, and that 140 places for medical students can be provided there, in addition to the 160 which already exist at the Colombo Medical College.

A flying doctor service in Nyasaland, organized by the Seventh Day Adventist Mission at Malamilo, is expected to start early this year.

At the instigation of the Maldon Society of Essex the council of the Royal College of Obstetricians and Gynaecologists has repaired the tomb of Dr. Peter Chamberlen in Woodham Mortimer churchyard.

People in the News

Oxford University has awarded the Osler Memorial Medal to Sir RUSSELL BRAIN, honorary fellow of New College, Oxford.

Sir HARRY SINDERSON PASHA has been appointed a knight of the Order of St. John of Jerusalem.

Professor SUBODH MITRA, dean of the medical faculty at Calcutta University, has been appointed vice-chancellor of the university.

COMING EVENTS

Milroy Lectures. — Dr. H. G. MILLER, "Accident Neurosis," February 7 and 9. Details on advertisement p. 63.

West End Hospital for Neurology and Neurosurgery.—Clinical demonstrations in neurology to be held at the hospital, 91 Dean Street, London W.1, February 7 to May 9. Details will be given weekly under "Societies and Lectures."

Family Planning Association.—Lecture discussions for senior medical students. Details on advertisement p. 62.

Hunterian Oration.—Sir RUSSELL BROCK, "Museum, Research, and the Inspiration of Hunter," February 14, 4 p.m., at Royal College of Surgeons of England, Lincoln's Inn Fields, London W.C.2.

Glasgow University and R.F.P.S. — Conference on "Atherosclerosis," March 8–10. Details on advertisement p. 62.

Postgraduate Medical School of London.—Advanced symposium, "Selected Topics in Chemical Pathology," April 18–20, at Postgraduate Medical School of London. Sessions: "Magnesium Metabolism," "Renal Failure," "Serum Enzymes," "Blocks in Intermediary Metabolism," "Instrumentation." Applications (fee £5 5s.) by March 22 to the Dean, Postgraduate Medical School of London, Ducane Road, London W.12.

Cambridge University School of Clinical Research and Postgraduate Medical Teaching.—Course, arranged by Professor R. A. MCCANCE, "Metabolic Disorders in Clinical Medicine," April 10–12. Details and registration forms from Secretary, Medical School, Tennis Court Road, Cambridge.

British Tuberculosis Association.—Meeting with Royal Netherlands Central Society for the Prevention of Tuberculosis, Amsterdam, April 21, 22. Details from Secretary of B.T.A., 59 Portland Place, London W.1.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH HEART JOURNAL

The Effects of Synthetic Angiotensin and Noradrenaline on Blood Pressure and Renal Function. E. G. McQueen and R. B. I. Morrison.
The Design of a Cardiac Defibrillator. R. J. Shephard.
Papilliferous Tumours of the Heart Valves. D. Heath, P. V. Best, and B. T. Davis.
Isolated Hypoplasia of the Right Ventricle and Tricuspid Valve in Siblings. W. E. Medd, H. N. Neufeld, W. H. Weidman, and J. E. Edwards.
Gout in Cyanotic Congenital Heart Disease. Jane Somerville.
Sub-clinical Rheumatic Carditis. R. Lannigan.
Maternity and Myocardial Failure in African Women. Harold Seftel and Mervyn Susser.
Pulseless Disease: A Report on Five Cases. R. A. Caldwell and E. W. Skipper.
A Current Concept of the Regulation of Blood Volume. James W. Pearce.
The Radiological Changes in Pulmonary Venous Hypertension, with Special Reference to the Root Shadows and Lobular Pattern. H. R. S. Harley.
Incisional Aneurysms of the Left Ventricle. W. F. Kerr, D. E. L. Wilcken, and R. E. Steiner.
Case Reports:
Coronary Artery Embolism. M. R. P. Hall and W. C. D. Richards.
Fatal Myocardial Infarction in a Youth of 15 Years. J. Syme and W. S. A. Allan.
Fallot's Tetralogy with some features of Marfan's Syndrome and Survival to 58 Years. A. S. Abraham, M. Atkinson, and W. M. Mitchell.

Volume 23, No. 1. (Bi-monthly; £4 4s. annually.)

GUT

Heredity in Gastroenterology: A Review. R. B. McConnell.
Clinical and Genetic Problems in Familial Intestinal Polyposis. A. M. O. Veale
The Distribution of Ulcerative Colitis and Regional Enteritis in United States Veterans, with Particular Reference to the Jewish Religion. E. D. Acheson.
An Assessment of the Value of Serum Cholinesterase as a Liver Function Test and in the Diagnosis of Jaundice. William Burnett.
Serum Albumin, Pseudocholinesterase, and Transaminases in the Assessment of Liver Function Before and After Venous Shunt Operations. Alan H. Hunt and Hermann Lehmann.
Aneurysm of the Splenic Artery. P. D. Bedford and Brian Lodge.
A Case of Spontaneous Rupture of the Normal Large Bowel Causing Haemoperitoneum. C. T. Howe.
The Use of Soframycin (Framycetin Sulphate) for Intestinal Sterilization. N. E. Stidolph and J. M. Alston.
The Augmented Histamine Test with Special Reference to Achlorhydria. Sheila T. Callender, F. P. Retief, and L. J. Witts.
Some Factors in the Assessment of Gastric Antisecretory Drugs by a Sampling Technique. J. B. Bingle and J. E. Lennard-Jones.
The Effect of an Adrenal Inhibitor (SU 4885) on Gastric Secretion in Dogs. J. W. McIntosh, N. Anderson, H. L. Duthie, and A. P. M. Forrest.
Intraoesophageal Adenocarcinoma. O. G. Dodge.
New Methods for Diagnosis and Research
Percutaneous Transhepatic Cholangiography. Michael Atkinson, Margaret G. Happey, and Francis G. Smiddy.
Radiological Investigation of the Small Intestine by Small Bowel Enema Technique. F. Pygott, D. F. Street, M. F. Shellshear, and C. J. Rhodes.
Gastroenterological Society of Australia.
Index to Volume 1.

Volume 1, No. 4. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 30

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. F. Goodwin: Bacterial Endocarditis

Tuesday, January 31

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. H. E. M. Kay: Transplantation of Haemopoietic Cells.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: Tumours Arising in the Dermis, Excluding Moles and Melanomata.
ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Manson Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., sherry party; 6.15 p.m., Mr. D. J. Newell: Demand for Hospital Beds.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Dr. A. W. Franklin: Care of the Premature Baby.

Wednesday, February 1

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Presidential Address by Dr. H. Neil Collier: If Not Accuracy, At Least Consistency.
BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTION.—At 36 Harborne Road, Edgbaston, 8.30 p.m., Dr. E. G. L. Bywaters: Neuropathic Joint Diseases and Rheumatoid Neuropathies.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: The Eosinophilic Granulomas of the Skin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. P. Lee Lander: Diagnosis of Carcinoma of the Lung.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. A. L. Jeanes: clinico-pathological conference.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. A. E. Francis: Problem of Cross-infection.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. F. G. J. Hayhoe: Cytology of Leukaemic Cells.

Thursday, February 2

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. C. B. Ford, Ph.D., D.Sc.: Inter-relationship of Nucleus and Cytoplasm.
LIVERPOOL MEDICAL INSTITUTION.—Joint meeting with Liverpool Psychiatric Club.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. F. W. Holdsworth: Injuries to the Spine.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Otolaryngology Lecture by Professor V. F. Lambert: Malignant Melanoma of the Nose.
ROYAL SOCIETY.—4.30 p.m., Professor W. D. M. Paton, F.R.S.: Theory of Drug Action Based on the Rate of Drug-receptor Combination.
ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Dr. W. M. Court Brown: Cytogenetic Studies in Human Leukaemias.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Maurice Partridge: postgraduate demonstration in psychiatry.

Friday, February 3

CAMBRIDGE UNIVERSITY: SCHOOL OF CLINICAL RESEARCH AND POSTGRADUATE MEDICAL TEACHING.—At Radiotherapeutic Centre, 4.15 for 4.30 p.m., Dr. P. J. Randle and Dr. R. M. Ehrlich: Diagnosis and Treatment of Pituitary Dwarfism.
GALENICALS.—At Royal Fort, Bristol, 5.30 p.m., Mr. G. M. FitzGibbon: Some Cosmetic Aspects of Plastic Surgery.
● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. S. Pegum: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. K. M. Citron: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. K. McLay: Surgical Treatment of Deafness.
NORTH-WESTERN THORACIC SOCIETY.—At Clinical Sciences Building, York Place, Manchester, 4.30 p.m., Dr. J. P. Anderson: Smoking; Mr. G. D. Jack: Oesophageal Hiatus.
PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields Hospital, 8.30 p.m., clinical evening.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Dr. David C. Sabiston, jun.: Surgical Aspects of Coronary Artery Disease. (2) 4 p.m., Professor J. McMichael.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Mr. D. L. Stevenson: An Inquiry into the Causation of Human Disease in General, and Cancer in Particular.

Saturday, February 4

MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 3 p.m., Mr. L. D. Abrams and Dr. W. A. Hudson: Heart Block and its Management.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—K. D. Allanby, M.D., M.R.C.P., Consultant Physician, Peterborough and Stamford Hospital Group; R. G. Gold, M.B., B.S., M.R.A.C.P., Senior Registrar in Cardiology, Regional Cardiological Centre, Papworth Hospital; A. D. George, M.B., B.S., F.R.C.S.Ed., F.R.F.P.S., Surgical Registrar, West Norfolk and King's Lynn General Hospital; G. E. Dimopoulos, M.B., Ch.B., Surgical Registrar (Casualty), Peterborough Memorial Hospital; B. V. Suryanarayana, M.B., B.S., F.R.F.P.S., D.T.M.&H., Medical Registrar, Peterborough Hospital Group; S. N. Budhraja, M.S., Surgical Registrar, North Cambridgeshire Hospital, Wisbech; A. R. Khan, M.B., B.S., D.T.M.&H., Registrar in Geriatric Medicine, South-west area of the Region; Judith J. Cuthill, M.B., B.Ch., Registrar in Psychiatry, Suffolk Mental Hospitals.
HUNTER, RICHARD A., M.D., M.R.C.P., D.P.M., Assistant Physician (Consultant status) in Department of Psychological Medicine, National Hospital, Queen Square, London, W.C.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Cole.—On December 17, 1960, to Margaret (formerly Whitham), M.B., Ch.B., and Brian W. Cole, M.R.C.S., L.R.C.P., of Carr House, Nottingham Road, Ripley, Derbyshire, a son—Andrew John.
Johnstone.—On December 4, 1960, at the Churchill Hospital, Oxford, to Sheila (formerly Godden), M.C.S.P., and Frederick C. Johnstone, B.M., B.Ch., a son—David Charles.
Smith.—On January 18, 1961, to Dr. Dorothy Lindsay (formerly Grieve), wife of Dr. Ian Inglis Smith, 15 Mansionhouse Road, Edinburgh 9, a son.

DEATHS

Adam.—On January 1, 1961, John Law Adam, M.B., F.R.C.S., of Far End, France Hill Drive, Camberley, Surrey, aged 94.
Broomhall.—On January 2, 1961, at Redlynch, Salisbury, Wilts, Benjamin Charles Broomhall, F.R.C.S., aged 85.
Denning.—On December 31, 1960, at his home, Birchington, Kent, Arthur Ffolliott William Denning, M.B., B.S.
Dowling.—On December 29, 1960, at his home, 388 Wilmslow Road, Withington, Manchester, Stephen Gerald John Dowling, M.B., Ch.B., also of Leaf Square, Pendleton, Lancs, aged 69.
Foskett.—On January 4, 1961, at Colorado Springs, U.S.A., Rev. Samuel Foskett, M.D., of Queen Anne's House, Taplow, Bucks, formerly of Harrogate, Yorks.
Fox.—On December 23, 1960, in hospital, William Allan Nesbitt Fox, F.R.C.S.I., of 70 Castle Park Road, Dun Laoghaire, Co. Dublin, late of Purley, Surrey.
Francis.—On January 2, 1961, at Boscombe Hospital, Douglas Ernest Francis, M.B., Ch.B., of 20 Bure Close, Mudeford, Christchurch, Hants.
Gregorson.—On January 20, 1961, Albert William Gregorson, M.D., F.R.F.P.S., of 17 Forestdale, Southgate, London N., and 20 Aubery Crescent, Largs, Ayrshire.
Moriarty.—On December 31, 1960, at Fleet, Hants, Thomas Bettesworth Moriarty, D.S.O., L.R.C.P.&S.I. and L.M., Lieutenant-Colonel, R.A.M.C., retired, aged 83.
Morton.—On December 29, 1960, Eva Morton, M.R.C.S., L.R.C.P.
Smith.—On December 17, 1960, at Reading, Berks, Neville Hardcastle Smith, D.S.C., M.R.C.S., L.R.C.P., of Buckhold Grange, near Pangbourne, Berks.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Phenothiazines and C.S.F. Protein

Q.—*A young man's C.S.F. twice had a protein content of 120 mg. %. On each occasion he was in a Parkinsonian state attributed to heavy medication with a tranquillizer (pre-tranquillizer lumbar punctures had shown no abnormality in C.S.F. protein). Smith[1] describes four mentally ill patients whose C.S.F. protein levels of 52 to 108 mg.% seemed to be causally related to a Parkinsonian state attributable to chlorpromazine therapy. I can find no subsequent confirmation, refutal, or qualification of this rather important potential diagnostic pitfall. Can you furnish me with any relevant data?*

A.—I have made inquiries on this subject, but there does not appear to be any information on the C.S.F. protein levels in patients who develop a Parkinsonian state while under treatment with phenothiazine drugs, other than the paper referred to. The point is an interesting and important one, and it would seem worth further investigation.

REFERENCE

1 Smith, J. K., *Amer. J. Psychiat.*, 1958, **115**, 167.

Potato Flour

Q.—*Is potato flour free from gluten? A patient on a gluten-free diet would find it very much easier if he could use potato flour.*

A.—Potato flour is free from gluten. An excellent account of gluten-free diets is given by Fletcher and McCririck.[1]

REFERENCE

1 Fletcher, R. F., and McCririck, M. Y., *Brit. med. J.*, 1958, 2, 299.

Injection of Hydatid Cysts

Q.—*(1) What is the best solution to inject into a hydatid cyst at operation to kill the daughter cysts and to prevent their spread into the peritoneal cavity after the cyst has been opened? Is 7% iodine in alcohol preferable to formalin solution? (2) If formalin solution is best, what strength of solution should be injected into the hydatid cyst? (3) What strength of formalin must be present within the cyst before the daughter cysts are killed, and how long should the solution remain in the cyst at operation before it is safe to open the cyst? (4) In countries such as Australia and Italy, where hydatid cysts are common, is it the usual procedure amongst surgeons there to inject formalin or 7% iodine in alcohol into their hydatid cysts at operation?*

A.—The solution with which most experience has been obtained and which has become standard in practice is 10% formol saline. It is generally considered to be the most rapidly acting and the most rapidly penetrating of the solutions available for killing and fixing tissue. Although 7% iodine in alcohol can be used for the purpose, it has no known advantages over the formalin solution. Sufficient formalin solution should be injected into the cyst to create a concentration of 3–4% formalin after the injection solution has been diluted by the fluid within the cyst. It may be necessary to aspirate some of the hydatid fluid, without rupturing the cyst, in order to achieve this end. The solution should remain in contact with the cyst contents for 5–10 minutes before they are removed from the patient.

It must be emphasized that injection of the cyst followed by aspiration of its contents at a single operation is more dangerous than marsupialization, which is recommended whenever some portion of the cyst wall can be brought to the body surface. It is there stitched to the edge of the wound, and, if the peritoneal cavity has been opened, the cut peritoneal edges are also stitched around the cyst. The exposed area of cyst is not opened until 48 hours after the operation, by which time the peritoneal cavity has become sealed off from the operation site and the cyst contents may be removed without fear of soiling the cavity.

Sensitivity to Varnish

Q.—*I was about to varnish a sailing dinghy with epoxy-resin, when I read an article in the Journal[1] in which it was stated that one could become sensitized during the mixing of such varnishes. Is it also possible to become sensitized to the finished, hardened varnish after it has been applied?*

A.—Sensitivity to the finished, hardened resin is very uncommon. Hardening is a process of polymerization; the polymer owes its valuable properties to the fact that it is chemically non-reactive and for this reason rarely affects the skin. Imperfect polymerization sometimes occurs, however, in which hardening seems to have taken place satisfactorily but some reactive molecules remain in the mass. When this occurs the finished and apparently hardened varnish may act as a sensitizer or may induce the eruption in a skin which has been previously sensitized. If good care is taken to prevent contact with varnish while varnishing a boat, the risk of trouble developing when using the boat later on is remote.

REFERENCE

1 *Brit. med. J.*, 1960, **2**, 1467.

Abacterial Cystitis

Q.—*All attempts to identify a causative infective agent for a persistent cystitis in a man aged 30 have failed. I.V.P. showed nothing abnormal; cystoscopy showed "cystitis and trigonitis." Chemotherapy and antibiotics have been ineffective. Can anything be done for this "abacterial cystitis"?*

A.—In general, any persistent cystitis in patients in this age group is tuberculous until proved otherwise. However, I presume that, although the patient has a sterile pyuria, repeated early-morning urine cultures for tubercle bacilli have proved negative. This leaves "Hunner's" ulceration (interstitial cystitis with ulceration), and a true abacterial pyuria. Hunner's ulcer is rare in men, but the diagnosis is made by excluding other causes and by repeated cystoscopic examinations.

Abacterial pyuria, perhaps occurring as one of the manifestations of Reiter's disease, where large joints and the conjunctivae may also be involved, is again diagnosed by exclusion, but it must be added that no urologist would commit himself without repeating the cystoscopy. Treatment in the absence of a firm diagnosis is obviously unsatisfactory, but it would be well worth while giving three injections of 0.3 g. of neoarsphenamine at three-day intervals.

Diphtheria Immunization in Adults

Q.—*A number of adults have recently requested immunization against diphtheria. What is the best and safest preparation to use, and should a Schick test be performed as a routine?*

A.—A preliminary Schick test should always be performed on persons over the age of 9 years. It is important that a watch be kept for "pseudo" reactors, who, if they require immunization, are the persons most likely to have sore arms after any of the available preparations. The early reading, at 24–48 hours, should not be omitted, since by the fifth to seventh day, when the second reading is made, the "pseudo" effect has faded considerably or disappeared.

The choice of prophylactics against diphtheria is largely a matter of personal preference. Formol toxoid (F.T.) has been recommended in order to reduce to a minimum the risk of development of "provocation" poliomyelitis; unfortunately it is a relatively weak prophylactic and less stable than the others. The mild vaccine toxoid antitoxin floccules (T.A.F.) also carries a very low risk of provocation

poliomyelitis, but it contains a small amount of horse serum to which a person might become sensitized. The most efficient prophylactics are alum-precipitated toxoid (A.P.T.) and purified toxoid aluminium phosphate (P.T.A.P.), which contain alum. Although the incidence of provocation poliomyelitis was higher (in the relatively small M.R.C. numbers[1]) with alum-containing preparations than with either F.T. or T.A.F., many doctors still prefer A.P.T. and P.T.A.P., especially in the poliomyelitis "off-season"—say from November to March. The British Army, however, prefers F.T. for adults. The modern trend is towards the use of combined prophylactics, and diphtheria and tetanus vaccine (DT/Vac) is a good one when primary immunization is necessary.

REFERENCE

[1] Report of the Medical Research Council Committee on Inoculation Procedures and Neurological Lesions: Poliomyelitis and Prophylactic Inoculations against Diphtheria, Whooping Cough, and Smallpox. *Lancet*, 1956, 2, 1223.

Transistorized E.C.G. Apparatus

Q.—*Is there any difference in the shape of tracings when using transistorized E.C.G. apparatus as compared with the conventional E.C.G. apparatus?*

A.—There is no difference in the shape of tracings when using transistorized direct-writing E.C.G. apparatus as compared with the conventional direct-writing type.

NOTES AND COMMENTS

Absorption of Oral Penicillins.—Dr. E. T. KNUDSEN (Beecham Research Laboratories, Ltd., Brentford, Middlesex) writes: I would like to comment on the answer to the question on the absorption of oral penicillins given in the *Journal* ("Any Questions?" November 26, p. 1615). In the reply to the question it is stated that: "No orally administered penicillin gives concentrations in the blood equalling those produced by the same dose of penicillin G given by injection." I cannot subscribe to this view. McCarthy and Finland's paper[1] on the absorption and excretion of four penicillins shows serum concentrations obtained in cross-over studies with, among other penicillins, phenethicillin by mouth and the potassium salt of benzyl penicillin by intramuscular injection. It will be seen in Table 8 of the paper that the peak serum concentrations in terms of μg./ml. of potassium penicillin G is 5.03 as opposed to 5.21 and 6.34 for phenethicillin. The authors discuss their results and on page 325 state that: "As compared with an equivalent dose of intramuscularly injected penicillin G, the peak concentration achieved by oral administration of phenethicillin is greater when assayed *in terms of drug given*, but is much lower when compared against the same standard and expressed in terms of units of penicillin G."

It is quite illogical to attempt to standardize new penicillins in terms of "penicillin G units" in the same way as it would be to try to standardize erythromycin, chloramphenicol, and the tetracyclines in such a manner. It could well be that a new penicillin had little activity against the Oxford staphylococcus and yet be highly active against proteus or *Ps. pyocyanea*; to attempt to standardize such a penicillin in terms of "penicillin G units" would be quite pointless.

The undeniable facts are that the oral administration of phenethicillin gives, in the vast majority of subjects, higher peak serum concentrations in terms of μg./ml. of the penicillin than following an equivalent dose of any other oral penicillin, or, indeed, following the intramuscular injection of the equivalent weight of benzyl penicillin.

REFERENCE

[1] McCarthy, C. G., and Finland, M., *New Engl. J. Med.*, 1960, 263, 315.

OUR EXPERT replies: Although Dr. Knudsen is right in saying that the peak level is higher, the levels at two and five hours were higher from penicillin given by injection. Apart from that he is perfectly right as regards absolute levels, although, as Finland has pointed out, penicillin by injection wins hands down in terms of activity against some important bacteria.

Anti-catarrh Vaccine.—Dr. J. MORRISON RITCHIE (Typhoid Research Unit, Georgetown, Demerara, British Guiana) writes: I have just seen a paragraph in the answer to the question on anti-catarrh vaccine ("Any Questions?" October 1, p. 1032). With the first part of the answer I am in entire agreement—i.e., where stock vaccines are condemned, as against autogenous. The second paragraph, which refers to my work published in 1958, is a complete misrepresentation, and suggests that whoever answered the question has not read the paper. In the first place, what are "saprophytic bacteria"? My paper was founded on the fact that normally saprophytic bacteria may become pathogenic if resistance be lowered by, say, a virus. The effect of an autogenous vaccine is therefore far from "incomprehensible," but merely common sense. It is not supposed that the virus itself is affected by an autogenous vaccine, the effect being to counter its depressing effects on the patient's resistance. Later work with antibiotics, ignored in your paragraph, has pointed the same way. There is, of course, no suggestion that the reticulo-endothelial system is involved at all. As the answer in your paper definitely misrepresents my article, I shall be glad if you will publish this disclaimer.

OUR EXPERT replies: I cannot admit that Dr. Ritchie has been misrepresented. The answer contains a faithful account of what he did, although it does not embody his interpretation of the results. That salivary bacteria become pathogenic when resistance is lowered by the cold virus is not a "fact" but an assumption on his part of which he has no proof.

Inheritance of Ichthyosis.—Dr. P. M. INMAN (Sunderland) writes: The rarity of very severe ichthyosis no doubt accounts for the difference of opinion expressed by your expert ("Any Questions?" October 22, p. 1252) and Drs. J. W. Platt and C. O. Carter (December 17, p. 1820). I personally have seen only one family affected by this disease, and the facts seem sufficiently important to describe briefly. In 1958 my paediatric colleague, Dr. Jackson, of North Shields, asked me to see a female child of 10 months who had been born with ichthyosiform erythrodermia without blisters. There was ectropion and eclabium and extreme thickening and scaling of the entire skin. The child was cared for exceptionally well by an intelligent and attentive mother and survived with very slow improvement. A second child was born to this mother in the summer of 1960, and I saw this child on the day after its birth. I was actually present as it died with a respiratory rate of 7 per minute and the similar gross ichthyotic skin changes which had been present in her sister. The mother was a young woman and these were her only two pregnancies. The skin of both parents was entirely normal and there was no history of any xeroderma in the family. If these children developed the disease owing to a recessive gene the mother must have been at a 25% risk at each pregnancy, and the chances against being unlucky twice running seem considerable. It is known that many of these children die in infancy, and I had thought that difficulty in chest movement was the cause of death in the second child as I watched it die. I understand the paediatric view is that this cannot be so because death from mechanical asphyxia would always show a rapid respiratory rate.

Muscular Dystrophy.—In the report of the symposium on current research in muscular dystrophy (January 21, p. 200) the name of Dr. J. Gibson's colleague should have been Miss Jennifer M. Jarvis.

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